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Primary Urinary Bladder Angiosarcoma with Osteoclast-Like Multinucleated Giant Cells: A Case Report and Literature Review

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Patient: Male, 68
Final Diagnosis: Urinary bladder angiosarcoma
Symptoms: —
Medication: —
Clinical Procedure: TURBT
Specialty: Diagnostics, Laboratory

Objective: Rare co-existence of disease or pathology
Background: Angiosarcoma is a fatal and aggressive mesenchymal tumor. It occurs in skin, breast, and parenchymal organs. It rarely arises primarily in the urinary bladder. Only 13 cases of primary urinary bladder angiosarcoma have been reported in the English literature.

Case Report: The patient was a 68-year-old man who presented to the Emergency Department with inability to void. Computed tomography of the abdomen and pelvis showed a urinary bladder mass. Surgical excision of the mass was performed. Pathological examination results were consistent with angiosarcoma. In addition to the unusual location of this tumor, the pathology was different from the previously reported cases in that this case was rich with osteoclast-like multinucleated giant cells.

Conclusions: The pathological diagnosis of primary urinary bladder angiosarcoma is challenging. Histological patterns and immunophenotypes are variable. Here, we review all reported cases of primary urinary bladder angiosarcoma, highlight the clinical and morphological features of this malignant neoplasm, and report a unique case of primary urinary bladder angiosarcoma with osteoclast-like multinucleated giant cells.

MeSH Keywords: Giant Cells • Hemangiosarcoma • Hematuria • Urologic Neoplasms

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Background

Primary urinary bladder angiosarcoma is an extremely rare mesenchymal tumor with only 13 reported cases [1,2]. It presents mainly in elderly men with hematuria. Histologically, the tumor consists of atypical anastomosing vascular channels in approximately 50% of cases. It is not uncommon for this tumor to dedifferentiate and form sheets of primitive cells, spindle cells, epithelioid cells, or a mixture of these cell types. The infrequency of such an entity in the urinary bladder, as well as the variation of histological appearance, constitutes a diagnostic challenge. Here, we review all reported cases of this neoplasm, highlighting the clinical presentation, histological features, immunophenotypic profile, and treatment. We present our case as the 14th reported case of primary urinary bladder angiosarcoma and the first primary urinary bladder angiosarcoma with osteoclast-like multinucleated giant cells.



Figure 1. CT scan of abdomen and pelvis showing urinary bladder mass.

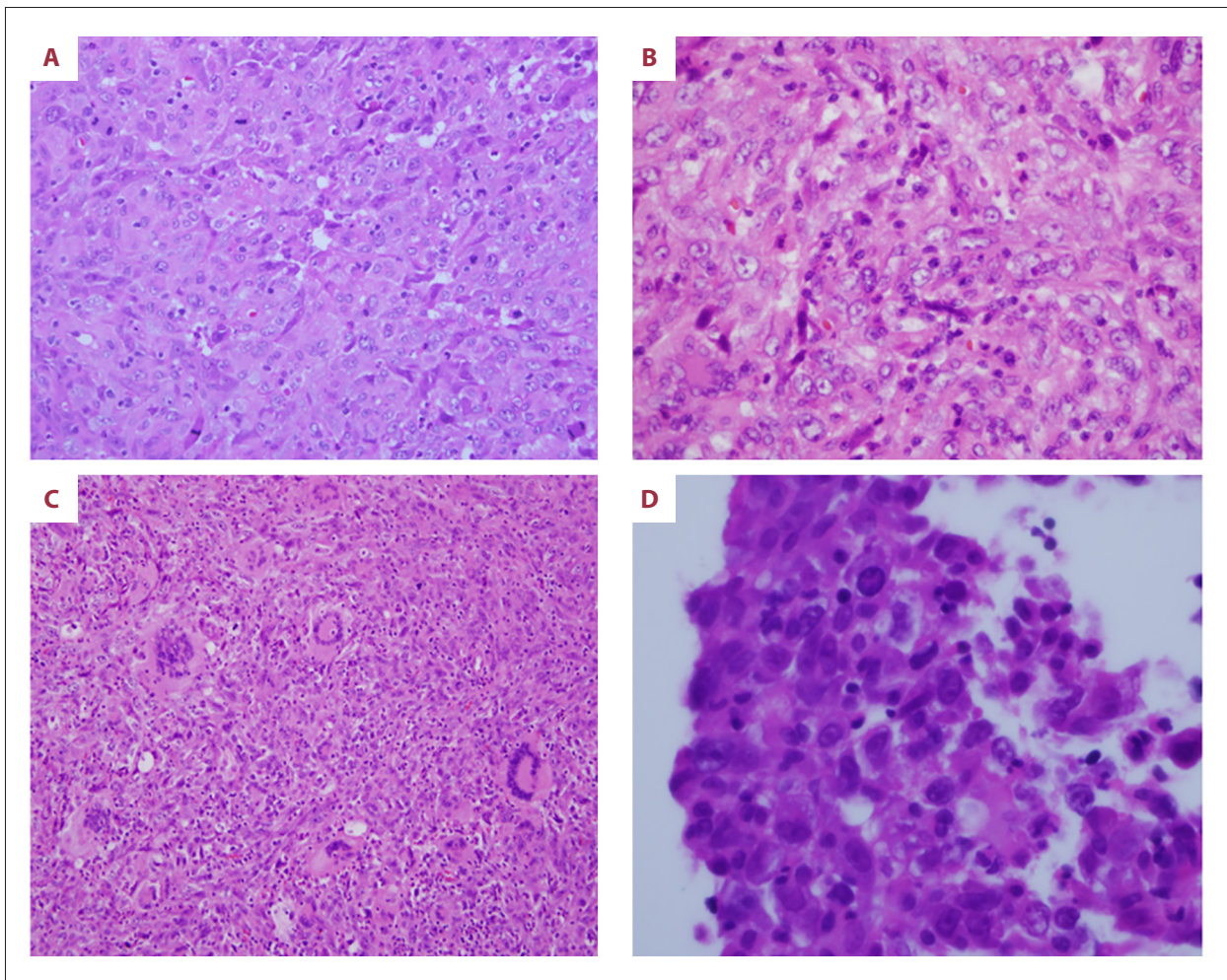


Figure 2. Representative H&E images. (A) (40×) Atypical spindle cells and epithelioid cells with mitotic figures. (B) (60×) Epithelioid cells with intracytoplasmic lumen. (C) (20×) Area with numerous multinucleated giant cells. (D) (60×) Cells with high nuclear cytoplasmic ratio.

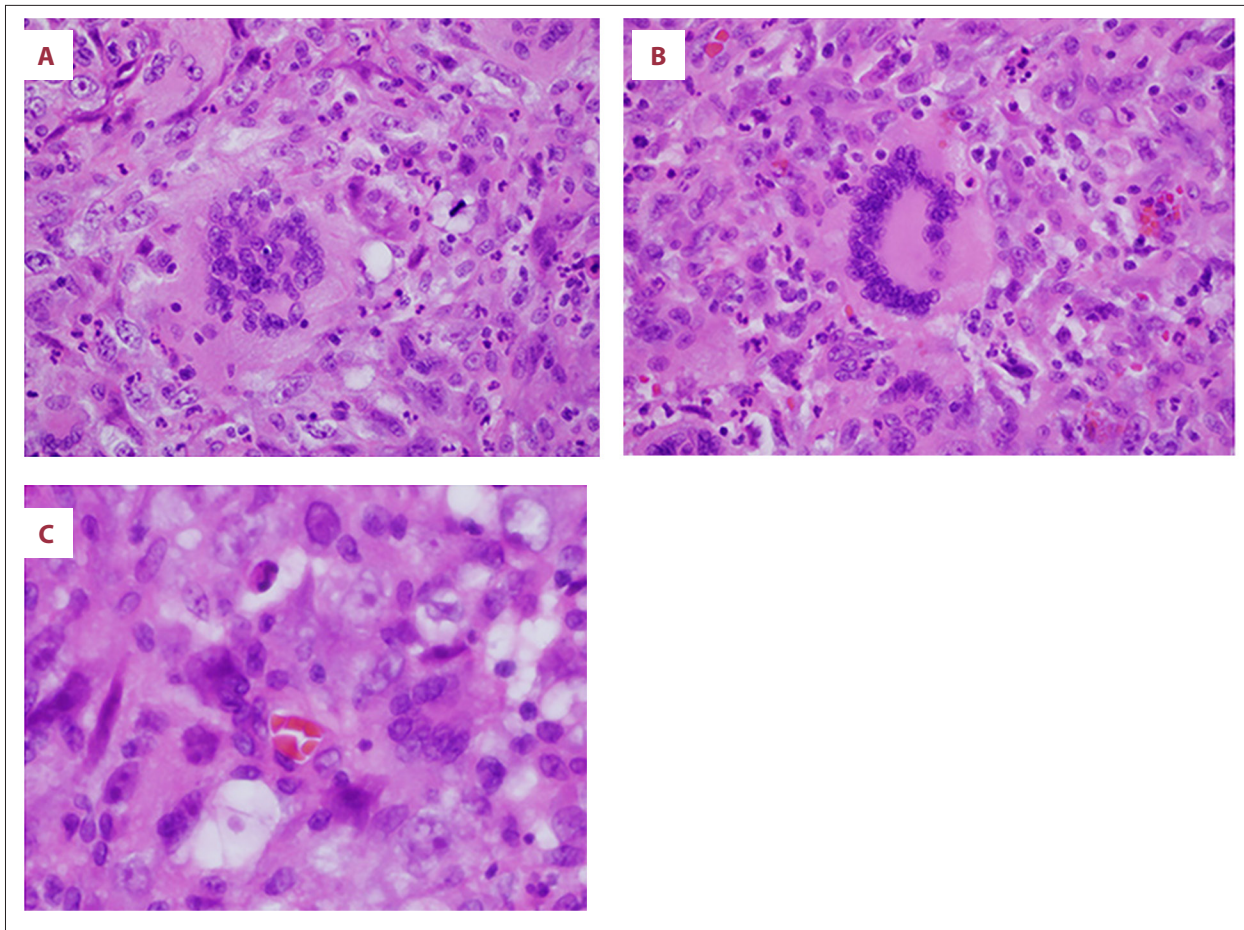


Figure 3. Features of multinucleated giant cells. **(A)** (60×) Multinucleated giant cell with up to 75 nuclei **(B)** (60×) Multinucleated giant cell with phagocytosed blood elements. **(C)** (60×) Questionable multinucleated giant cell with intracytoplasmic lumen.

Case Report

Clinical features

A 68-year-old white male presented to the Emergency Department (ED) with a chief complaint of inability to void, abdominal pain, fever, and unintentional weight loss for 6 weeks duration. The patient had a known history of congenital hypospadias, diverticulosis, and frequent ED visits with urinary outflow obstruction. The history was negative for malignancy and radiotherapy. Laboratory studies were significant for leukocytosis and high creatinine level. Computed tomography of the abdomen and the pelvis showed a distended urinary bladder with large filling defect on the left lateral wall of the urinary bladder with bilateral hydronephrosis (Figure 1). The radiological appearance of the mass was worrisome for a malignant process. A urinary catheter was placed and 2000 ml of urine with white debris and sediments were evacuated. The patient was admitted for transurethral resection of a bladder tumor (TURBT). The intra-operative course was complicated by limited visibility secondary to the large tumor burden,

bleeding, and excessive necrotic debris. The tumor encased the urinary bladder and the prostate. The tumor was sent for pathology examination.

Pathologic examination

Gross description

The received tissue weighed 185 g and consisted of an aggregate of tan-pink fragments of soft tissue admixed with blood. No normal prostatic tissue or urinary bladder mucosa was identified. A total of 14 sections were submitted for microscopic examination.

Microscopic description

The tissue consisted of solid sheets of cells with areas of acute inflammation, hemorrhage, and necrosis. Three populations of cells were identified: spindle cells, epithelioid cells, and multinucleated giant cells. The spindle cells and epithelioid cells were highly atypical, with high nuclear cytoplasmic ratio, and

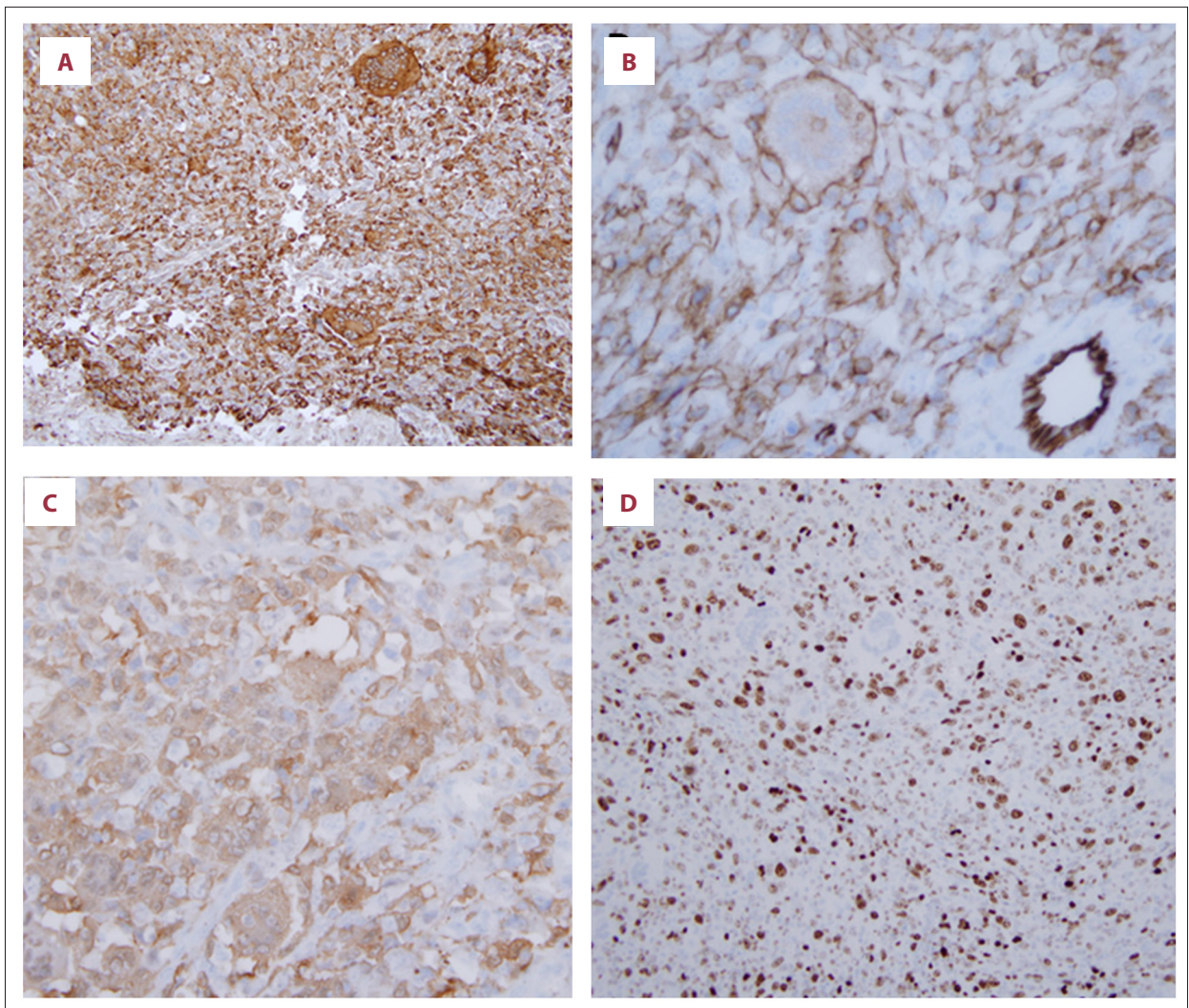


Figure 4. Immunophenotypic features. (A, B) Cells express CD68 (left) and CD31 (right). (C) Patchy staining with factor XIII. (D) Ki-67 is expressed in approximately 40% of cells and is not expressed by the multinucleated giant cells.

hyperchromasia, as well as prominent and multiple nucleoli and atypical mitotic figures. Some of the epithelioid cells had intracytoplasmic lumens. The tumor had scattered multinucleated giant cells (Figure 2); these were osteoclast-like with up to 75 nuclei, phagocytosed blood elements, and no mitotic activity. Rare questionable intracytoplasmic lumens were noted in the multinucleated giant cells (Figure 3). No urothelial or prostatic tissues were identified.

The differential diagnoses based on the morphological findings were poorly differentiated carcinoma, melanoma, high-grade lymphoma, and high-grade sarcoma. To narrow the differential diagnoses, we used immunohistochemistry as ancillary testing.

The tumor was tested with epithelial cell markers (GATA-3, CK7, prostate-specific antigen, prostate-specific alkaline phosphates, CK5/6, and P63), melanoma markers (S-100, Mart-1,

and HMB-45), and lymphoma markers (LCA, CD20, CD3, CD30, and ALK-1). Other used markers included Ki-67, CD68, vimentin, and vascular markers (factor XIII and factor VIII).

Results

Tumor cells, including the multinucleated giant cells, were diffusely positive for vimentin, CD31, and CD68 and focally positive for factor XIII. Ki-67 was positive in about 40% of the tumor cells and it was negative in the multinucleated giant cells (Figure 4). The tumor cells were negative for all other markers. Given the pathological features combined with the immunophenotypic features, the diagnosis of primary urinary bladder angiosarcoma was rendered.

Table 1. Summary of reported primary urinary bladder angiosarcoma cases.

Year/author	Age	Sex	Predisposing factor/ significant history	Main symptom	Histology/ expressed markers	Treatment	Outcome
1907/ Jungano, [1,2,4]	54	M	Hemangioma	Urinary obstruction and Hematuria	Anastomosing vascular channel/NIP	S	NAD
1970/ Casal et al., [1, 2, 4]	85	F	Hemangioma	Hematuria	Anastomosing vascular channel/NIP	S	Myocardial infarction, Died 3 days after diagnosis
1987/ Stroup and Chang [1,2,4]	68	M	NAD	Hematuria	Anastomosing vascular channel/FVIII	S	Metastasis to lung and liver, Myocardial Infarction. Died 8 months after diagnosis
1991/ Aragona et al. [1,2,4]	78	M	NAD	Hematuria	Anastomosing vascular channel/ FVIII, UEA1	S	Myocardial infarction, died 2 months after diagnosis
1993/ Ravi [1,2,4]	55	M	NAD	Hematuria	Anastomosing vascular channel/NIP	S & RT	Alive and free of disease 8 months after diagnosis
1997/ Navon et al. [1,2,4]	78	M	R 13 years prior to diagnosis	Hematuria	Anastomosing vascular channel/ CD34, FVIII	S	Alive and free of disease 30 months after diagnosis
1998/ Engel et al. [1,2,4]	47	M	NAD	Hematuria	Solid, primitive, epithelioid/NIP	S, C & R	Alive and free of disease 29 months after diagnosis
1999/ Schindler et al. [1,2,4]	47	M	NAD	Dysuria and left flank pain	Solid, Anastomosing vascular channel, epithelioid/CD31	S	Lymphatic spread
2006/ Seethala et al. [1,2,4]	66	M	R 4 years prior to diagnosis	Hematuria	Solid, primitive, epithelioid and spindle/CD31, CD34	S & C	Questionable peritoneal metastasis Alive and well at 19 months after diagnosis
2007/ Kulaga et al. [1,2,4]	83	F	R 14 years prior to diagnosis/ endometri-oid adenocarcinoma.	Hematuria	Epithelioid angiosarcoma/CD31		
2008/ Williams et al. [1,2,4]	71	M	R 10 years prior diagnosis/ prostate cancer	Hematuria	Epithelioid angiosarcoma/CD31, CD34, and Factor VIII	S, R & C	Abdomen diffuse carcinomatosis, died 3 months postoperatively.
2011/ Warne et al. [3]	32	F	None/ 6 months postpartum	Hematuria	Epithelioid angiosarcoma/CD31, fVIII-related antigen, ULEX, CD34, AE1/ AE3, Cam5.2, CK8, MNF116, CK20	S, Paclitaxel	Lung metastasis, died 19 months after diagnosis
2015/ Bahouth [1,2,4]	89	M	R 12 years ago/ prostate cancer	Hematuria	Anastomosing vascular channel/ CD31, CD34, factor VIII	S & R	Metastasis to spinal vertebrae and pelvic bone, died 3 months after diagnosis
Current/ Nawar	68	M	None/ Hypospadias	Urinary obstruction	Sheets of spindle cells, epithelioid cells and osteoclast like multinucleated giant cells/CD31, CD68	S	Died 3 weeks postoperatively

NAD – no available date; NIP – no immunohistochemical studies performed; C– chemotherapy; R – radiotherapy; S – surgery.

Clinical follow-up

Post-operatively, the patient's urethral catheter was repeatedly obstructed with necrotic tumor tissue. Aggressive therapy was recommended to the patient, including radical cystoprostatectomy with urethrectomy followed by chemotherapy and radiotherapy, but the patient refused further treatment and elected to go home with hospice care. The patient died 6 weeks after hospital discharge.

Discussion

Angiosarcoma of the urinary bladder is a malignant tumor that mimics the morphology and function of endothelium. It can be primary or secondary to direct extension or metastasis. Primary urinary bladder angiosarcomas are very rare. Thirteen cases of primary urinary bladder angiosarcoma (PUBA) have been reported in the English literature [1,2].

Our review of the 13 reported cases indicated that primary urinary bladder angiosarcoma (PUBA) occurs in males more often than females, with a ratio of 3:1, and the patients have a median age of 68 years at diagnosis. Patients commonly present with hematuria. Other symptoms include: flank pain, suprapubic pain, and dysuria. The etiology of PUBA is unknown. Radiotherapy and hemangioma are seen in association with PUBA in 38% and 15% of cases, respectively.

Grossly, PUBA is described as large hemorrhagic mass with areas of necrosis. The histopathology of PUBA is variable. The typical histology of angiosarcoma with anastomosing vascular channels is seen in PUBA in about 53.5% of cases. The epithelioid variant was described in 23% of cases. In about 30.8% of cases, the tumor consisted of sheets of primitive cells, some mixed with epithelioid cells, and some with a focus of typical histology. The immunophenotypic features are also variable; therefore, a panel of immunostains, including CD31, CD34, factor XIII, and factor VIII, is necessary. Of the reported cases, 7 showed positive staining with factor VIII and 2 were negative. CD34 staining was positive in 5 cases and was negative in 2 cases. CD31 staining was performed in 5 cases and it was positive in all of them [1–4] (Table 1).

As very few cases of this malignancy have been reported [2,5,6], there is no consensus treatment algorithm. Due to the aggressive nature of the tumor, the primary treatment modalities consist of resection of the tumor with a radical cystectomy, also including the prostate, urethra, vagina, or any other structures that have been invaded. Radical cystectomy with lymph node dissection followed by chemotherapy and radiation therapy is the recommended therapy [1,6]. Chemotherapy regimens that have been performed include Ifosfamide and

epirubicin followed by single-fraction radiation therapy [3]. Adequate tumor resection and margin status are important determinants of survival [7]. Despite the aggressive therapy noted in the literature, long-term survival is poor. The longest documented survival after multimodal therapy is 6 years [8].

Factors that made the diagnosis of PUBA challenging in this case were the unusual clinical presentation and unusual histology. This patient presented with symptoms of urinary tract obstruction rather than hematuria. In addition, the patient had no prior exposure to radiation, as opposed to the 38% of reported cases.

Histologically, the tumor was poorly differentiated and was rich with osteoclast-like multinucleated giant cells. These cells were immunophenotypically similar to the tumor cells in the expression of vimentin, CD31, and factor XIII. The presence of osteoclast-like multinucleated giant cells in this case with the described immunophenotype is unique. Giant cells have been described in association with urothelial carcinoma *in situ*, invasive papillary carcinoma, high-grade infiltrating urothelial carcinoma, sarcomatoid carcinoma, and choriocarcinoma of the bladder [9]. To the best of our knowledge this is the first reported case of PUBA with osteoclast-like multinucleated giant cells. The role of these cells in PUBA is not yet clear.

Conclusions

Primary urinary bladder angiosarcoma is a rare and an aggressive malignant neoplasm. It has a male predominance and commonly presents with hematuria. Exposure to radiotherapy is associated with PUBA in 38% of cases. The pathogenesis of PUBA is not yet understood. The pathology is that of typical angiosarcoma in only half of the cases. In atypical cases, testing with immunohistochemistry is essential. Markers expressed in angiosarcoma include CD31, CD34, factor VIII, and factor XIII. Treatment requires surgical excision and postoperative radiotherapy and chemotherapy. The prognosis is poor.

For the pathologist, diagnosing this entity is challenging, especially in cases with atypical morphology. Pathologists should have a high index of suspicion in elderly men presenting with hematuria and a urinary bladder mass. The absence of a history of radiotherapy does not exclude angiosarcoma from the differential diagnoses list.

Here, we presented a unique case of primary urinary bladder angiosarcoma with osteoclast-like multinucleated giant cells. These cells have been described in association with urinary bladder carcinoma. This is the first case report describing osteoclast-like multinucleated giant cells in urinary bladder angiosarcoma and it is the 14th reported case of primary

urinary bladder angiosarcoma. More research is necessary to understand the role of osteoclast-like multinucleated giant cells in urinary bladder neoplasm in general and in angiosarcoma in particular.

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