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Ewing-like sarcoma bladder primary tumour: A case report and literature review

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ABSTRACT

Bladder primitive neuroectodermal tumors are extremely rare but are most frequent in older adult.

59-year-old man that complained of hematuria for the previous 24 h, urethral syndrome, and pain in the right renal fossa over the previous two weeks.

No definitive management or treatment guidelines have been established. Hematuria is the most frequent symptom. Advanced age, metastasis, and incomplete tumor resection are determinants of a poor prognosis.

Ewing-like bladder primary tumor is a rare entity with a poor prognosis, hence an aggressive treatment combining surgery and chemotherapy must be considered from the beginning.

1. Introduction

Both Ewing and Ewing-like sarcoma are aggressive tumors characterized by the presence of neoplastic, round mesenchymal cells, which are most frequent in children and young adults.[1] Ewing-like tumors represent a morphologically and molecularly heterogeneous group of neoplasms that are histologically similar to Ewing sarcoma but without the presence of canonical fusions between the *EWSR1* gene and members of the ETS family of transcription factors.[1]

Three main types of Ewing sarcomas have been described: bone, extraosseous, and primitive neuroectodermal tumors (PNET).[2] Incidence of these tumors' peaks in children and young people aged 10–20 years, with an incidence of 3 cases per million under the age of 20.[3]

On the other hand, bladder PNET are extremely rare but are most frequent in older adults.[4] Just 19 cases of bladder PNET have been described in the literature, and most were diagnosed at advanced stages, when the tumor was invasive or metastatic, resulting in a poor prognosis.

This study presents a case of Ewing sarcoma/primary bladder PNET that was muscle-invasive and metastatic at the time of diagnosis.

2. Case report

A 59-year-old man presented to the emergency department (ED) in September 2020, complaining of hematuria for the previous 24 h, urethral syndrome (dysuria – pain during micturition -, increased urinary frequency and vesical tenesmus), and pain in the right renal fossa over the previous two weeks. Related to his personal history, he had a smoking habit (with an approximate exposure to tobacco of 31.5 pack-years).

The patient had an acute deterioration of the kidney function, with creatinine (Cr) levels of 1.76 mg/d, hence a scan was performed. Fig. 1 (abdominopelvic computed tomography (CT) scan without contrast) revealed a grade II right hydroureteronephrosis, secondary to a bladder lesion on the right posterolateral wall (42 mm × 35 mm). A transurethral resection of the bladder was scheduled.

In the extended study, consisting of a chest-abdominal-pelvic CT with contrast, lytic lesions suggestive of metastasis were found on the left pubic branch, iliac bones, L4, and on the vertebral body of D11, D8, D7 and D1.

The anatomopathological study showed parietal invasion (including

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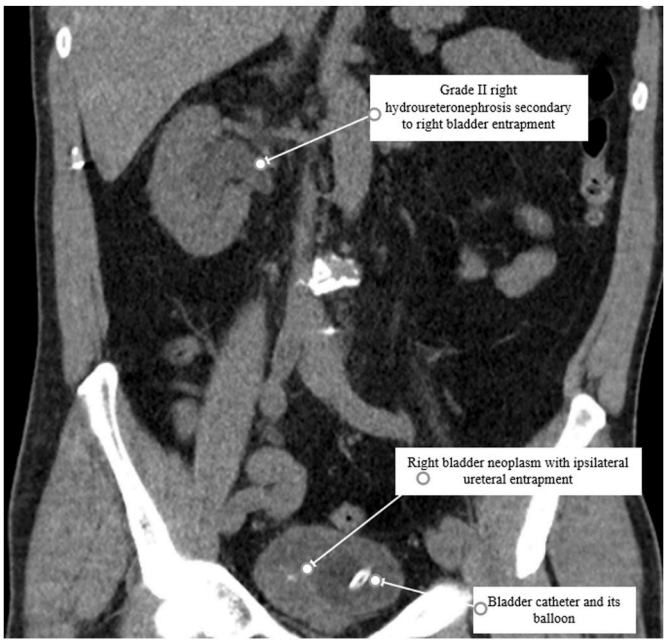

Fig. 1. Abdominopelvic computed tomography (CT) scan without contrast that reveals a grade II right hydroureteronephrosis, secondary to a bladder lesion on the right posterolateral wall.

the muscular layer) by a malignant tumour, which presented a dense proliferation of small, round basophils, with scant cytoplasm and hyperchromatic, rounded nuclei. In Fig. 2A–2D (immunohistochemical study) cells showed an intense diffuse membrane positivity on CD99 (Fig. 2A), as well as for vimentin (Fig. 2B). Cells also presented an intense diffuse membrane positivity to neuron-specific enolase (NSE) (Fig. 2C). In the other hand, positivity was not observed for cytokeratins (Fig. 2D).

A more detailed immunohistochemical study was then required, with the rest of the biomarkers assessed also showing negative results: CKAE1.AE3 (excluding poorly differentiated carcinoma); **chromogranin and synaptophysin (excluding a neuroendocrine tumor);** and OCT3/4 (excluding a germ cell tumor).

After obtaining the anatomopathological findings, the case was brought to the multidisciplinary urooncology board, with specialists in oncology, urology, radiology, onco-radiotherapy, medical physics, and anatomical pathology. Board members agreed on a treatment plan based on systemic chemotherapy. Hence, the patient received systemic

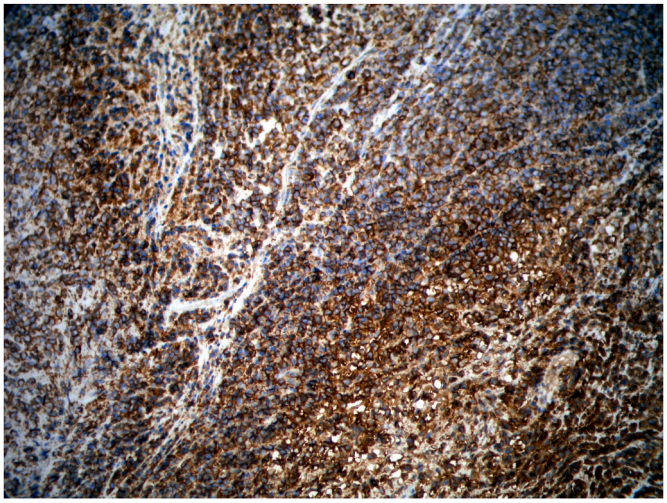

Fig. 2A. Inmunohistochemical study shows immunoreactivity to CD 99.

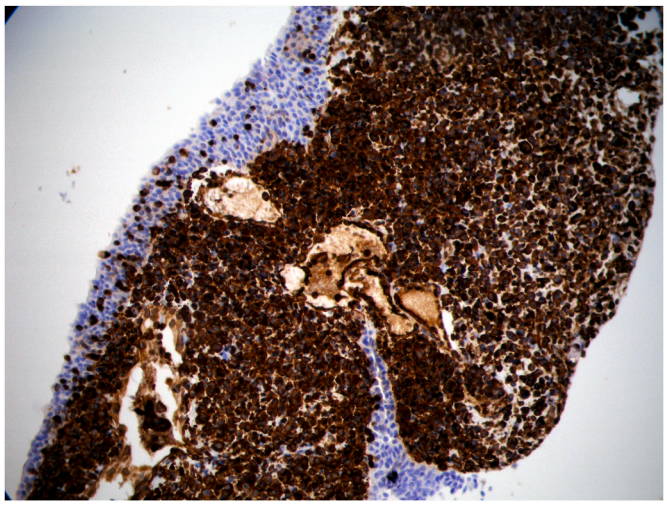

Fig. 2B. Inmunohistochemical study shows immunoreactivity to vimentin.

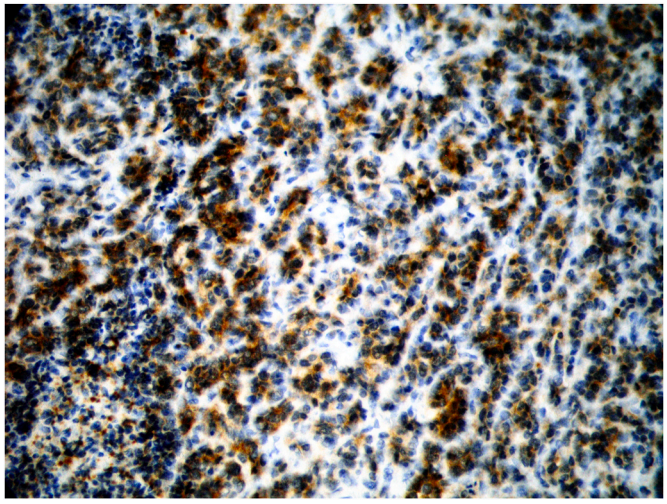

Fig. 2C. Inmunohistochemical study shows immunoreactivity to neuron-specific enolase (NSE).

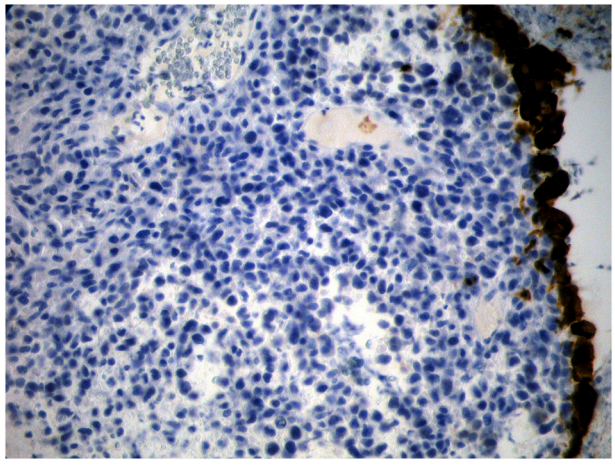

Fig. 2D. Inmunohistochemical study showed no immunoreactivity to cytokeratins.

treatment with chemotherapy schedule consisting on vincristine 2 mg (day 1), doxorubicin 75 mg/m2 (day 1), cyclophosphamide 1200 mg/m2 (day 1) + mesna (detoxifying agent) for 21 days. Prior to the fourth chemotherapy cycle, a PET-CT control scan showed a partial response to treatment.

During the outpatient follow-up in the oncology service, the patient showed a septic state, severe leukocytosis (90% neutrophilia), procalcitonin of 25 ng/mL, C-reactive protein of 40 mg/dL, coagulopathy (Quick index 56%), severe deterioration of kidney function (Cr 5.06 mg/dL), and mild hyponatremia and hyperpotassemia.

An abdominopelvic CT without contrast revealed right hydroureteronephrosis, prompting an emergency urinary diversion through a right percutaneous nephrostomy.

Despite the urinary diversion, the patient's general condition further deteriorated, with no improvement in kidney function along with worsening hydroelectrolytic alterations that led to a hypocalcemic state. Ionic and antibiotic corrective measures could not prevent multiorgan failure, which ended in the patient's death.

3. Literature review and discussion

Because bladder PNET is a very rare cancer, no definitive management or treatment guidelines have been established. This extremely aggressive, malignant tumor originates in the migratory embryonic cells of the neural crest, appearing predominantly in adults.[3]

To date, just 19 cases of bladder PNET have been described in the literature, so most information on its management has been gleaned from experience with Ewing sarcoma. Table 1 (Bladder Ewing's Sarcoma described in the literature to date) summarizes the published cases; patients' age ranges from 10 to 81 years, with a mean of approximately 42 years.

Regarding the clinical presentation, hematuria is the most frequent symptom, followed by dysuria, increased frequency of urination, and hydronephrosis. There were no differences between sexes, with 8 published cases in men (with ours, 9) and 11 in women.

Molecular tests with fluorescent in situ hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) have shown an *EWS/FLI-1* gene fusion in some patients with PNET.[4] The protein resulting from this fusion, generated by the translocation of t (11; 22) (q24; q12), may be one pathogenic factor in the development of a PNET.[5]

Based on the cases of bladder PNET reported to date, it appears that advanced age, metastasis, and incomplete tumor resection are determinants of a poor prognosis. Of the 20 reported cases, 8 (40%) were

Table 1
Published cases of primitive neuroectodermal tumor (PNET) of the bladder to date.

Study	Age/ Sex	Symptoms	Size (cm)	Metastasis	Surgery	Adjuvant therapy	Survival
Banerjee et al (1997)	21/M	Frequency, dysuria, hematuria	8 × 6 × 4	No	Cystectomy	Chemotherapy (VAC)	≥18 months
Gousse et al (1997)	15/F	Hematuria	3 × 2 × 2	No	TURBT	Chemotherapy (VAC + IE)	≥18 months
Desai (1998)	38/F	Hematuria	12 × 7 × 3.5	No	Cystectomy + hysterectomy + double adnexectomy	-	-
Mentzel et al (1998)	62/M	Choluria, fever, lumbago, AUR	14 × 10 × 10	Rectum and retroperitoneum	TURBT + nephrostomy	No	Died at 2 weeks
Colecchia et al (2002)	61/F	Hydronephrosis and kidney failure	-	Lungs	-	-	-
Kruger et al (2003)	81/M	Lymphedema, fatigue, urgency, incontinence, hydronephrosis	-	Pelvis and retroperitoneum	TURBT + nephrostomy	No	Died at 2 weeks
Ellinger et al (2006)	72/M	Hematuria, oligoanuria	-	Frozen pelvis, ileum	TURBT	-	≥2 months
Lopez-Beltran et al (2006)	21/F	Frequency, dysuria, hematuria	9 × 8 × 6	No	Cystectomy + hysterectomy + double adnexectomy	Chemotherapy + imatinib	≥36 months
Osone et al (2007)	10/M	Dysuria and hematuria	1	No	TURBT	Chemotherapy (CDV + IE)	≥2 years
Al Meshaan et al (2009)	67/F	Hematuria, fever, hydronephrosis	3 × 2.5 × 1	Pelvic and pulmonary adenopathies	TURBT + partial cystectomy	Chemotherapy	Died at 8 months
Rao et al (2011)	14/F	Lower abdominal lump and dull pain	15 × 12 × 7.5	No	Partial cystectomy	Chemotherapy	≥6 months
Busato et al[17]	52/F	Frequency, dysuria, pelvic pain, hematuria	3.3 × 1.5 × 2.2	No	TURBT	Chemotherapy (VAC + IE)	≥27 months
Okada et al (2011)	65/M	Hematuria and dysuria	5	Lungs	TURBT + cystectomy	Chemotherapy (VIDE) + radiotherapy	Died at 22 months
Zheng et al (2011)	74/M	Frequency, dysuria, hematuria		No	TURBT	Chemotherapy (VAC)	Died at 4 months
Sueyoshi et al (2014)	10/M	Polyuria, edema of lower abdomen	13.5 × 13.1 × 12.9	No	JJ catheter + partial cystectomy	Chemotherapy (VAC + IE)	≥11 months
Lam et al (2016)	30/F	Polyuria, hematuria	6.4 × 9.4 × 7.7	No	TURBT + cystectomy + Indiana reservoir	Chemotherapy (VAC + IE)	
Tonyali et al (2006)	38/F	Hematuria	4 × 2.6 × 2.5	No	TURBT + cystectomy + HT	Chemotherapy (VAC + IE)	≥14 months
Vallonthaiel et al (2011)	27/F	Frequency, hematuria	10.3 × 9.8 × 4.7	Pelvic adenopathies	TURBT	Chemotherapy (VAC)	≥3 months
Gao L et al (2020)	45/F	Frequency, urgency, dysuria	3	No	TURBT + cystectomy + hysterectomy	Chemotherapy (VAC)	≥24 months
Present study (2020)	59/M	Hematuria, dysuria and pain in right renal fossa	4 × 3.5 × 4	Multiple lytic and pulmonary lesions	TURBT + nephrostomy	Chemotherapy (VAC)	Died at 4 months

AUR: acute urinary retention; **TURBT**: transurethral resection of bladder tumour; **VAC**: vincristine, actinomycin D, cyclophosphamide; **IE**: ifosfamide, etoposide; **CDV**: cyclophosphamide, pirarubicin, vincristine; **VIDE**: vincristine, ifosfamide, doxorubicin, etoposide.

diagnosed with regional or distant metastasis: 4 of those (50%) presented involvement of the pelvic or retroperitoneal lymph nodes; 1 (12,5%), regional or metastatic involvement of the ileum and rectum; and 4 (50%), metastasis to the lungs. Of the 8 patients with metastatic disease, 5 (62,5%) died after an average of 7 months post-surgery (range 0.5–22 months), confirming the poor prognosis and low survival of patients with metastatic disease at diagnosis.

In conclusion, Ewing or Ewing-like bladder primary tumor is a rare entity with a poor prognosis, hence an aggressive treatment combining surgery and chemotherapy must be considered from the beginning. Nevertheless, more cases must be published and analyzed for establishing a protocolized guideline for the treatment of this disease.

Authors contributions

NAKDALI KASSAB, B: Writing – original draft, Writing – review and editing, PÉREZ-SEOANE BALLESTER, H: Conceptualization, Methodology, SARRIÓ SANZ, P: Resources, SÁNCHEZ CABALLERO, L: Methodology, GÓMEZ GARBERÍ, M: Visualization, ORTIZ GORRAIZ, M: Writing – review and editing. Supervision.

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