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

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A B S T R A C T

Bladder primitive neuroectodermal tumors are extremely rare but are most frequent in older adults. A 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, extracranial, 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 hydronephrosis, 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, lyric 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
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
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), hypercalcitonin 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.

During the inpatient stay, the patient showed a septic state, 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.

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. 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.

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.     | 21/M     | Frequency, dysuria, hematuria   | 8 × 6 × 4 | No         | Cystectomy               | Chemotherapy (VAC)     | ≥18 months          |
| (1997)              |          |                                 |           |            |                          |                        |                     |
| Goussé et al.       | 15/F     | Hematuria                       | 3 × 2 × 2 | No         | TURBT                    | Chemotherapy (VAC + IE)| ≥18 months          |
| (1997)              |          |                                 |           |            |                          |                        |                     |
| Desai (1998)        | 38/F     | Hematuria                       | 12 × 7 × 3.5| No         | Cystectomy + double adnexectomy |                        |                     |
| Mentzel et al.      | 62/M     | Choluria, fever, lumbago, AUR   | 14 × 10 × 10| Rectum and retroperitoneum | TURBT + nephrostomy |                        | Died at 2 weeks |
| (1998)              |          |                                 |           |            |                          |                        |                     |
| Colecchia et al.    | 61/F     | Hydronephrosis and kidney failure |          | Lungs |                        | -                      |                      |
| (2002)              |          |                                 |           |            |                          |                        |                     |
| Kruger et al.       | 81/M     | Lymphedema, fatigue, urgency, incontinence, hydronephrosis |           | Pelvis and retroperitoneum | TURBT + nephrostomy |                        | Died at 2 weeks |
| (2003)              |          |                                 |           |            |                          |                        |                     |
| Ellinger et al.     | 72/M     | Hematuria, oligoanuria          |           | Frozen pelvis, ileum | TURBT                  |                        | ≥2 months          |
| Lopez-Beltran et al.| 21/F     | Frequency, dysuria, hematuria   | 9 × 8 × 6 | No         | Cystectomy + hysterecomy + double adnexectomy | Chemotherapy + imatinib | ≥36 months          |
| (2006)              |          |                                 |           |            |                          |                        |                     |
| Osono et al.        | 10/M     | Dysuria and hematuria           | 1         | No         | TURBT                    | Chemotherapy (CDV + IE)| ≥2 years            |
| (2007)              |          |                                 |           |            |                          |                        |                     |
| Al Meshaan et al.   | 67/F     | Hematuria, fever, hydronephrosis | 3.5 × 2.5 × 1 | Pelvic and pulmonary adenopathies | TURBT + partial cystectomy | Chemotherapy       | Died at 8 months   |
| (2009)              |          |                                 |           |            |                          |                        |                     |
| 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. 47    | 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   |
| Suyoshi 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 + HTIE | Chemotherapy (VAC + IE) | ≥14 months         |
| Vallonthai et al. (2011)| 27/F | Frequency, hematuria              | 10.3 × 9.8 × 4.7 | Pelvic adenopathies | TURBT | Chemotherapy (VAC) | ≥3 months          |
| Gao et al. (2020)   | 45/F     | Frequency, urgency, dysuria      | 3         | No        | TURBT + cystectomy + double adnexectomy | 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, SARRÍO SANZ, P: Resources, SÁNCHEZ CABALLERO, I: Methodology, GÓMEZ GARBERÍ, M: Visualization, ORTIZ GORRAIZ, M: Writing – review and editing. Supervision.

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