CASE REPORT

Clear cell adenocarcinoma of the bladder with intravesical cervical invasion

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SUMMARY

A 26-year-old woman with a complicated urological and gynecological history with uterine didelphys with bilaterally inserting intravesical cervical oses presented with cyclical haematuria. Work up revealed a mass in the ectopic cervical os and adjacent bladder wall. Subsequent resection confirmed a clear cell adenocarcinoma of urological origin with invasion into neighbouring os.

BACKGROUND

Prune belly syndrome (PBS), a rare congenital condition, is seldom reported in female patients. While the coexistence of PBS and cloacal anomaly (CA) has been previously reported,¹ no reports of concomitant PBS and uterus didelphys (UD) with cervical insertion into the bladder currently exist in the literature. We present a case of a 26-year-old woman with PBS, CA and UD, who developed clear cell adenocarcinoma of the bladder invading an ectopic cervix.

CASE PRESENTATION

A 26-year-old Afghani woman presented with cyclical haematuria. She had no available documentation of her initial neonatal care in Afghanistan. Diagnosis was thus made retrospectively based on history given by the patient and her family, and additionally on physical examination when urological care was sought for recurrent pyelonephritis at age 3 in the USA. Evaluation demonstrated evidence of multiple genitourinary congenital anomalies: PBS (lack of rectus abdominii and dilated ureters for which the patient had undergone abdominal wall repair and bilateral ureteral reimplantation), CA (long urethra with retracted meatus, creation of a bowel-based neovagina, and imperforate anus requiring bowel pull-through), and UD. In the US, she underwent reduction cystoplasty and redo bilateral ureteral reimplantation. The patient was sporadically compliant with clean intermittent catheterisation and suffered from recurrent bladder stones requiring periodic cystoscopic treatment.

The patient was transiently lost to follow-up until the onset of menarche, when she experienced cyclical, menstruation-related haematuria. Further investigation with examination and imaging led to diagnosis of the aberrant insertion of her cervical oses, and her menses was successfully managed with oral contraceptives.

TREATMENT

At age 27, the patient experienced 'breakthrough', off-cycle haematuria despite menstrual suppression, severe enough to require blood transfusion. She was referred for urological evaluation and on cystoscopy had an area of inflammation of the left bladder floor. Biopsy revealed clear cell adenocarcinoma. Immunohistochemistry staining was positive for hepatocyte nuclear factor-1, PAX-8 and Ki-67, showing a high proliferation index. There was insufficient information, however, to establish a genitourinary versus gynaecological origin.

Subsequent MRI revealed bilateral partially duplicated collecting systems and a mass immediately posterior to the bladder wall, appearing to arise from the left cervix. Imaging also revealed inguinal lymphadenopathy. Staging positron emission tomography/CT redemonstrated left posterior bladder wall thickening and a hypermetabolic right inguinal node, with no pulmonary or skeletal metastases. Inguinal node biopsy confirmed presence of clear cell adenocarcinoma. Immunohistochemically, the tumour cells were positive for uroplakin, PAX8, CK7 and Cam5.2, and negative for estrogen receptor, progesterone receptor, CDX2, CK20 and P63. Accordingly, a urinary tract origin was favoured, but given the patient's complicated anatomy, no definitive diagnosis could be established.

In the context of these findings, a repeat cystoscopic evaluation and examination under anaesthesia were performed. Cystoscopy showed obvious tumour progression in the left trigone; bimanual examination demonstrated a hard nodular mass palpated at the base of the neovagina, which was not fixed to the pelvic sidewalls.

The patient's symptoms progressed, with worsening abdominal pain and haematuria, requiring admission and transfusion. Given her young age

Figure 1 Specimen showing uterus didelphys with two separate insertions into the urinary bladder (arrows).

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Figure 2 Urinary bladder revealing bilaterally inserting cervical ora (arrows).

and progressive symptoms, the patient was offered anterior exenteration with ileal conduit urinary diversion (figures 1 and 2) with subsequent inguinal lymphadenectomy. Gross, intraoperative findings revealed a didelphic uterus with dilated left horn (consistent with outflow obstruction) and insertion of bilateral cervixes into the bladder. At the left cervical insertion, in the left lateral wall of the bladder near the trigone, a 3 cm tumour was noted. There was no pelvic sidewall invasion. This gave the tumour the gross appearance of a cervical adenocarcinoma.

Final pathology demonstrated poorly differentiated (G3) clear cell adenocarcinoma of the urinary bladder with negative margins. Detrusor muscle invasion was present without invasion into the perivesical fat. Extension into the left uterine orifice without invasion of myometrium or endometrium was noted. The bladder mucosa away from the tumour showed non-keratinising squamous metaplasia. The right ovary, each uterine corpus and fallopian tubes were histologically unremarkable. Metastatic adenocarcinoma was observed in 1 of 17 lymph nodes. Immunohistochemistry staining was positive for CK7 and uroplakin, focally positive for CK20 and negative for p16, a pattern supporting a genitourinary tumour origin (figure 3).

DISCUSSION

PBS has a reported incidence of 1 in 40 000 live births, with only 5% of cases occurring in females. It is characterised by the absence of abdominal wall musculature, cryptorchidism and with collecting system abnormalities. CA occurs in roughly 1 in 50 000 births and represents up to 10% of congenital anorectal abnormalities in females.² Anomalies of reproductive organs, such as bicornuate uterus and CAs, have been observed

separately in females with PBS.³ UD—a condition resulting from a failed fusion of the medial walls of Müllerian ducts—leads to pairs of uterine cavities and cervixes. Although cervical insertions are necessarily ectopic, their intravaginal insertion is usually preserved. The constellation of PBS, CA and UD, particularly with bilateral cervical insertion into the bladder, has not been previously reported.

Development of bladder neoplasia is known to occur in association with these congenital anomalies; our search revealed two reported cases of PBS linked with nephrogenic adenoma, and reports of CA presenting with cloacogenic carcinoma, adenocarcinoma and, most infrequently, squamous cell carcinoma of the bladder.^{4–6} Particularly unique in this patient is the cervical involvement by the adenocarcinoma of the bladder, a pathological occurrence that has not been previously reported. Whether this is embryological or circumstantial is unclear.

Clear cell adenocarcinoma of the urinary bladder is one of the rarest histological variants of bladder cancer, and predominantly affects women.⁷ The exact embryological root remains controversial, with competing theories proposing urothelial versus Müllerian origins.^{8–9} In this patient, the coexistence of congenital Müllerian and CAs makes both histological origins equally plausible. The atypical abutment of urothelium and cervical mucosa further clouded the pathological diagnosis, requiring extensive immunohistological staining before identifying clear cell adenocarcinoma of the bladder as a final diagnosis.¹⁰

Learning points

- ▶ Patients with multiple congenital anomalies present a particularly difficult population for surveillance and diagnosis of urological malignancies owing to their atypical anatomy and multiple risk factors.
- ▶ Cyclical haematuria in a woman of reproductive age should raise suspicion for ectopically inserting cervical os.
- ▶ Haematuria in patients with a complicated urological history should inspire an increased level of suspicion for urological malignancy.
- ▶ Physicians involved in these patients' care must maintain a high index of suspicion and must counsel patients of the need for close, routine monitoring of urinary function and symptoms.
- ▶ Given the complexity of precise diagnoses in such cases of atypical anatomy, elective partial or complete removal of affected organs should be considered.

Figure 3 (A) Infiltrating poorly differentiated adenocarcinoma of the bladder. The tumour is composed of irregular poorly formed cords of tumour cells with clear cytoplasm. Calcifications are present within the tumour. There is lymphovascular permeation by tumour cells present (arrow); magnification $\times 30$. (B) Infiltrating adenocarcinoma in the uterine cervix with tumour cells showing clear cytoplasm; magnification $\times 30$.

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Contributors DM conceptualised and designed the study, collected data and analysed data, drafted the initial manuscript and approved the final manuscript as submitted.

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