CASE REPORT

Urothelial carcinoma with villoglandular differentiation (UCVGD) with small cell neuroendocrine carcinoma of urinary bladder

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SUMMARY

Urothelial carcinoma with villoglandular differentiation (UCVGD) is a rare aggressive variant of urothelial carcinoma. It is usually associated with high-grade urothelial carcinoma or rarely adenocarcinoma. There is only one other previous report of UCVGD associated with small cell neuroendocrine carcinoma of urinary bladder. We report the second case of UCVGD with small cell neuroendocrine carcinoma of urinary bladder in a 74-year-old non-smoker male patient. The mass was muscle invasive and also invaded the prostate. This entity needs to be confidently diagnosed due to its prognostic and therapeutic implications.

BACKGROUND

Urothelial carcinoma with villoglandular differentiation (UCVGD) is a rare variant of urothelial carcinoma. The entity is difficult to diagnose in the limited biopsy sample. Its association with small cell neuroendocrine carcinoma of urinary bladder is previously reported in only one case. We reported this case highlighting its aggressive behaviour, difficulty in diagnosis and its prognostic significance.

CASE PRESENTATION

A 74-years-old non-smoker man presented with hesitancy and difficulty in passing urine for 1 month. This was followed by an episode of haematuria. The patient was a known hypertensive (on amlodipine). On examination, the abdomen was soft and non-tender, and no mass could be palpated. Digital rectal examination revealed hard prostate.

INVESTIGATIONS

The complete blood count and renal function tests were within normal limits. The prostate specific antigen (PSA) level was 0.27 ng/mL (normal range 0–4 ng/mL). Urine culture revealed methicillin-sensitive *Staphylococcus aureus* infection, for which the patient was treated with adequate antibiotics.

Ultrasonography of kidney, urinary bladder and prostate (USG-KUBP) showed a solid hypoechoic mass lesion arising from the left lateral wall of the urinary bladder with extension into the paravesical region measuring about 6×5.8 cm (figure 1A). The wall thickness of the urinary bladder was 3 mm and the postvoid residual urine measured 20 cc. The prostate measured 3.8×3.6×3.3 cm (approximately 23

g) and was mildly enlarged in size with normal echotexture. The kidneys measured 9.2 cm (right) and 8.8 cm (left), respectively, and showed distinct corticomedullary junction without any evidence of hydronephrosis or alteration of the echotexture. Contrast-enhanced CT abdomen and pelvis revealed a large polypoidal heterogeneously enhancing exophytic mass arising from anterior wall of the urinary bladder which measured 7.1×5.4×5.0 cm (figure 1B). Anteriorly, the mass was projecting into the perivesical space, adjacent pelvic peritoneum along with the parietal wall. Posteriorly, the mass showed an intraluminal bulge in the bladder lumen. Inferiorly, the mass showed indistinct fat planes with the anterior aspect of the prostate and the pubic bones. There was no definite infiltration of the bowel loops, ureters or vesicoureteric junction. No locoregional or para-aortic lymphadenopathy was noted. X-ray chest and contrast-enhanced CT chest did not reveal any mass lesion in the lungs (figure 1C). A cystoscopy was performed with the possibility of an invasive urothelial carcinoma of bladder and a mass was seen involving the anterior wall, dome and the left lateral wall of the urinary bladder. Transurethral biopsy transurethral resection of bladder tumour (TURBT) was obtained from the tumour located over the dome of bladder along with a finger-guided prostatic biopsy.

The TURBT sample showed multiple fragments of tan grey chips weighing 1.0 g in total. The prostatic biopsy comprised three linear cores ranging in size from 0.5 to 1.5 cm in length. The histopathological examination of the TURBT chips showed a tumour with two different histomorphological areas (figure 2A). The predominant area (90%) showed an infiltrative tumour arranged in anastomosing cords and trabeculae, lobules and groups and at places in diffuse sheets with interspersed areas of necrosis (figure 2B). A tiny focus also showed a few rosettes. The tumour cells were separated by scant stroma. They were relatively monomorphic with high N:C ratio, oval to elongated hyperchromatic nuclei, granular chromatin, inconspicuous nucleoli and scant amount of cytoplasm. Brisk mitosis and numerous apoptotic bodies were of note (figure 2C). Moulding and crushing artefacts were also seen. Morphologically, the dominant part of the tumour appeared to be small cell

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Figure 1 (A) Ultrasonography of kidney, urinary bladder and prostate showing a solid hypoechoic mass in the bladder (B) The contrast-enhanced CT abdomen showing an infiltrative large polypoidal exophytic mass arising from the anterior wall of the urinary bladder and extending into the anterior abdominal wall. (C) The chest X-ray did not reveal any shadow suggestive of any mass lesion.

neuroendocrine carcinoma. Rest of the areas showed villoglandular architecture with high-grade nuclear morphology of the lining columnar cells, calcification and inspissated eosinophilic secretion in the glandular spaces (figure 2D,E) overlying a focus of invasive tumour having nests of polygonal cells with centrally placed oval nuclei, nuclear pleomorphism, coarse chromatin, moderate amount of pale eosinophilic to clear cytoplasm and well delineated cell membrane (figure 2F). This focus of invasive tumour was morphologically different than the small cell carcinoma in the immediate vicinity. Hence, about 90% of the invasive foci showed small cell carcinoma morphology with about 5% area showing high-grade urothelial morphology. Other 5% area showed villoglandular architecture. The lining urothelium showed urothelial carcinoma in situ changes. Tiny bit of detrusor

Figure 2 (A) Scanner view photomicrograph highlighting villoglandular and small cell neuroendocrine components of the tumour ($\times 20$). (B,C) The small cell neuroendocrine area arranged in the form of anastomosing cords and trabeculae with interspersed areas of necrosis (B; $\times 100$). The cells showed hyperchromatic nuclei, scant cytoplasm, numerous mitoses and apoptoses (C; $\times 200$). (D,E) The villoglandular area showed villous architecture and interspersed glandular areas, calcification and inspissated secretion (D; $\times 100$); the lining cells were columnar with high-grade dysplasia (E; $\times 200$). (F) The invasive high-grade urothelial component showing polygonal clear cells, different from the small cell or villoglandular components ($\times 40$) (H&E stain).

Figure 3 Immunohistochemistry showing positivity for synaptophysin (A; $\times 100$) and chromogranin (B; $\times 200$) in the small cell neuroendocrine component. GATA3 was positive in the high-grade urothelial area but negative in the small cell neuroendocrine area (C; $\times 100$). Villoglandular area showed variable intensity nuclear positivity for GATA3 (D; 100x), CDX2 (E; $\times 400$) and membranous positivity for CK20 (F; $\times 100$).

included in this biopsy was infiltrated by the small cell carcinoma component. The core biopsy from the prostate showed a tumour with small cell carcinoma morphology with interspersed benign prostatic glands. None of the biopsies showed any malignant glandular component. Immunohistochemistry was performed in both the TURBT chips as well as in the prostatic cores. The small cell neuroendocrine carcinoma component in urinary bladder and prostate showed granular cytoplasmic positivity for synaptophysin (figure 3A) and chromogranin (figure 3B), the former being more diffuse than the latter. The small cell carcinoma component was negative for GATA3 (figure 3C), PSA, CDX2 and CK20. In contrast, the invasive high-grade urothelial component showed strong nuclear positivity for GATA3 and variable intensity membranous positivity for CK20. CDX2, PSA, synaptophysin and chromogranin were negative in the invasive high-grade urothelial areas. The villoglandular component showed focal strong nuclear positivity for GATA3 (figure 3D) and CDX2 (figure 3E) and variable intensity membranous positivity for CK20 (figure 3F). PSA, synaptophysin and chromogranin were negative in the villoglandular areas. β -catenin showed membranous positivity in all the components (small cell carcinoma, high-grade urothelial carcinoma and villoglandular) although the percentage positivity and the intensity were variable.

A diagnosis of UCVGD with small cell neuroendocrine carcinoma of bladder was rendered. The tumour showed infiltration of the lamina propria, detrusor muscle and the prostate.

DIFFERENTIAL DIAGNOSIS

The pathologists face considerable diagnostic difficulty in assessing the nature of a villoglandular area. A villoglandular area transitioning into a high-grade urothelial carcinoma can be easily diagnosed as an essential component of UCVGD. In contrast, a villoglandular area not continuing into urothelial carcinoma cannot be assumed to be a component of UCVGD and it can also be a part of a coexisting incidentally detected/sampled villous adenoma similar to the index case. Hence, histomorphologically, we considered both the diagnoses, a small cell neuroendocrine carcinoma with a minor component of high-grade invasive urothelial carcinoma coexisting with a villous adenoma of urinary bladder and a UCVGD coexisting with a small cell neuroendocrine carcinoma. The urothelial component can be a part of UCVGD and/or small cell neuroendocrine carcinoma in the second scenario. The other consideration was

obviously a carcinoma of prostatic origin infiltrating the bladder. Consequently, we resort to a wide panel of immunohistochemistry. The positive staining for neuroendocrine markers (synaptophysin and chromogranin), negative PSA stain and focally positive GATA3 in the invasive high-grade urothelial component supported the diagnosis of small cell neuroendocrine carcinoma with a component of urothelial carcinoma. The index case showed a high-grade villoglandular area with focal nuclear GATA3 positivity. It also showed focal CDX2 positivity and relative lack of membranous β -catenin positivity suggesting the villoglandular component to be a part of UCVGD. The absence of nuclear β -catenin positivity also rules out a primary colonic origin of the tumour.

TREATMENT

The major implication of diagnosing UCVGD with small cell neuroendocrine carcinoma is in its treatment. This is the second case report in English literature and there is no standard treatment protocol. We believe that the small cell neuroendocrine component is the most aggressive one among the three and a radical cystoprostatectomy combined with platin-based neoadjuvant chemotherapy could be beneficial.

OUTCOME AND FOLLOW-UP

The patient is planned for neoadjuvant chemotherapy followed by the radical cystoprostatectomy.

DISCUSSION

UCVGD is a rare variant of urothelial carcinoma. There are only two case series and two case reports of UCVGD in the English literature along with description of urine cytology in UCVGD.¹⁻⁵ Small cell neuroendocrine carcinoma of bladder comprises <1% of all bladder tumours.^{6,7} It is an aggressive variant of urothelial carcinoma and postulated to be arising from the urothelium by divergent differentiation. UCVGD had been shown to be associated with invasive high-grade urothelial carcinoma in the previous reports by Lim *et al*, Mitra *et al* and Tajima and Koda.^{1,3,4} However, there was only one previous report of UCVGD associated with small cell neuroendocrine carcinoma in the English literature and this case was also described by Lim *et al*.¹ Hence, we believe that this is the second case depicting a UCVGD associated with a muscle-invasive small cell neuroendocrine carcinoma.

Adult urothelium is known for its ability to undergo phenotypic differentiation.⁸ Urothelial carcinoma with divergent differentiation is a fairly common occurrence in uropathology. This property has been attributed to the embryological origin of the bladder from the multipotent tissues of the cloacal endoderm and the mesodermal Wolffian ducts.⁹ Stem cell theory with divergent differentiation is also in vogue.¹⁰ Small cell neuroendocrine carcinoma constitutes about 0.5%–0.7% of the malignant bladder tumours.⁶ Historically, it had been postulated to originate from the neuroendocrine cells in the urinary bladder.⁷ However, its more than often association with high-grade urothelial carcinoma merits an alternate explanation. It is now considered to have a urothelial origin. Indeed, in the study conducted by Cheng *et al*, molecular genetic evidence of common clonal origin of small cell carcinoma of the urinary bladder and urothelial carcinoma with a multipotential, undifferentiated cell or stem cell of origin was suggested.¹¹ We believe that the association of UCVGD with high-grade urothelial carcinoma and/or small cell neuroendocrine carcinoma supports the theory of divergent differentiation. In fact, the index case showed the presence of

a small cell neuroendocrine component, villoglandular component and an invasive high-grade urothelial component.

This is the second case of UCVGD associated with small cell neuroendocrine carcinoma in the English literature. The previous case was seen in a 62-year-old female patient and in that case a high-grade papillary urothelial carcinoma coexisted with the small cell component and a superficial micropapillary component. The same case showed a depth of invasion up to the perivesical soft tissue implying an aggressive course and poor outcome.¹ The index case also showed a prostatic infiltration and detrusor involvement. The extravesical spread could not be commented on microscopy (TURBT sample). However, there was no radiological evidence of extravesical spread. Overall, the index case reinforces our previous findings in the form of marked male predominance, old age group and muscle-invasive nature of UCVGD indicating poor prognosis. In addition, this case also shows prostatic invasion worsening the prognosis and compounding the differential diagnosis.

The implication of this case is manifold. It depicts the importance of identification a minor villoglandular area in a tiny biopsy/limited sample. It should alert the pathologist of a high-grade urothelial carcinoma in the immediate vicinity irrespective of a negative sample. In such cases, a repeat biopsy could be beneficial. The second importance lies in the morphological and immunohistochemical distinction between the villoglandular component of an incidental Villous adenoma (VA) and a UCVGD. VA can be cured by simple excision, had adenocarcinomatous focus not been found. In contrast, a radical surgery is often needed for UCVGD. The prognostic implications of VA and UCVGD are entirely different, the former being an entirely benign tumour. A judicious use of immunopanel is advisable and necessary in these situations. This case also signifies the pathway of divergent variation of urothelial carcinoma and merits special mention mainly due to poor prognostic value. Lastly, this case is a mere diagnostic challenge for a pathologist and poses significant challenge for the treating clinician as there is no standard treatment protocol.

Learning points

- ▶ Urothelial carcinoma with villoglandular differentiation (UCVGD) is an extremely rare and aggressive variant of urothelial carcinoma.
- ▶ Histomorphologically, urothelial carcinoma, usually high grade coexists with villoglandular area that needs to be distinguished from a villous adenoma, a benign entity.
- ▶ Even rarer is the coexistence of a small cell neuroendocrine carcinoma with UCVGD, both of which are highly aggressive neoplasm of the urinary bladder.
- ▶ Rarity of this entity precludes a standard mode of treatment, although platin-based chemotherapy coupled with radical cystoprostatectomy could be the optimal option.
- ▶ Histopathologists need to be aware of the rare entity as it has both diagnostic, therapeutic and prognostic implications.

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