Introduction: Although the tumors are often easily detected, a considerable number of patients with female urethral carcinoma are diagnosed in an advance stage. Thus, no evidence-based therapeutic approach has been established. We herein report our experience in the treatment of three female patients with urethral carcinoma. We also examined the expression of PD-L1 and CTLA-4.

Case presentation: Three female patients pathologically diagnosed with urethral carcinoma, including urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma, between 2013 and 2017 were analyzed in this study. Two patients underwent urethrectomy with cystostomy. Immunohistochemistry was performed to assess the levels of PD-L1 and CTLA-4 expression in patients with urethral carcinoma. Eleven control cases of urethral carcinoma tissue were also stained.

Conclusion: This study revealed the expression of PD-L1 and CTLA-4 in female urethral carcinomas.

Key words: CTLA-4, female urethral cancer, immunocheckpoint inhibitor, PD-L1.

Keynote message

All female urethral carcinoma expressed both PD-L1 and CTLA-4 regardless of pathological type.
Case presentation

Case 1
An 83-year-old woman visited our department with a chief complaint of gross hematuria. A solid round mass, 1 cm in its diameter, was palpable right below the external urethral orifice. A fine needle biopsy was performed; the pathological diagnosis was SCC. We recommended surgical resection, but she declined surgery due to her old age.

Case 2
A 70-year-old woman visited gynecology clinic in our institution with a chief complaint of a palpable mass right below the external urethral orifice. We resected the mass that was 1.5 cm in diameter. The pathological diagnosis was AC (Skene gland origin). The detailed information has been reported previously.3

Case 3
A 65-year-old woman visited gynecology clinic in our institution with a chief complaint of brown menses. Transvaginal ultrasonography revealed a 15-mm mass between the urethra and vagina (Fig. 1). A transperineal needle biopsy was performed and a pathological examination led to the suspicion of UC. The clinical stage was cT2N0M0. We initially planned neoadjuvant systematic chemotherapy with the aim of achieving the complete resection of the urethral tumor. After six courses of gemcitabine and cisplatin chemotherapy, urethrectomy was performed along with cystectomy. The final

Fig. 1 (a) Contrast-enhanced CT, (b) positron emission tomography-CT, (c) T1WI of MRI, (d) T2WI of MRI, (e) diffusion image of MRI, and (f) sagittal T2WI of MRI. CT and positron emission tomography-CT revealed a 26 × 14-mm urethral tumor. MRI revealed a 30 × 20-mm urethral tumor between the vagina and urethra.
pathological diagnosis was UC, pathologically T2, with a negative surgical margin (Fig. 2). She was free of recurrence 8 months after the surgery.

Immunostaining

We immunohistochemically examined the expression of PD-L1 and CTLA-4 in the above three tumors as well as 11 female cases of urethral carcinoma (four SCCs, four ACs, and three UCs) included in a tissue microarray (UR1001; US Biomax, Rockville, MD, USA). Immunostaining and its scoring were performed, as we described previously, using antibodies to PD-L1 (company) and CTLA-4 (company). The levels of PD-L1 and CTLA-4 expression are summarized in Table 1 (Fig. 3). All the present three female tumors showed weak (1+) expression of PD-L1. The UC (Case 3) showed weak (1+) expression of CTLA-4, whereas the SCC (Case 1) and the AC (Case 2) showed strong (3+) expression of CTLA-4. There was no significant distribution in PD-L1 and CTLA-4 expression between male and female tumors. Although the number of cases included in the tissue microarray was relatively small, PD-L1 was expressed in 100.0% of UCs and 75.0% of SCCs, and 75% of ACs. All of the histological subtypes expressed CTLA-4, and strong (3+) expression was seen in 66.7% of UCs, 75.0% of SCCs, and 100.0% of ACs.
Discussion

The European Association of Urology guideline recommends surgical resection in combination with neoadjuvant chemotherapy for the management of advanced urethral carcinoma. This systemic chemotherapy is found to be effective in 72% of cases and is associated with prolonged overall survival. However, no further postoperative therapies that significantly improve patient outcomes have been established. In one of our cases, we performed surgical resection followed by six courses of neoadjuvant gemcitabine and cisplatin chemotherapy. No apparent recurrence was observed in 14 months after the surgery in this case.

Anti-PD-L1 antibody treatment was approved by the U.S. Food and Drug Administration as a second-line chemotherapy for UC in 2016. PD-L1 is expressed in some of urothelial cancers and exhibits an antitumor effect by suppressing activation of T cells or the anti-tumorigenic immune system. Both anti-PD-L1 and anti-CTLA-4 antibodies have been shown to suppress tumor progression through these mechanisms. Currently available molecular markers are insufficient to predict the potential for tumor recurrence and progression precisely. PD-L1 is expressed on antigen-presenting cells, such as human monocytes, as well as activated human and murine dendritic cells. PD-L1 is a corregulatory ligand that can inhibit immune responses by either binding to PD-1 or a putative non-PD-1 receptor on the surface of T lymphocytes to induce antigen-specific T-cell apoptosis.

This study examined the expression of both PD-L1 and CTLA-4 in female urethral carcinomas. Our three cases, UC, SCC, and AC, all expressed PD-L1 (all 1+) and CTLA-4 (all 3+). These staining results were similar to those in other female urothelial cancers included in a purchased tissue microarray. These findings suggest that immune checkpoint inhibitors may be useful in the treatment of female urethral carcinoma.

Conclusion

PD-L1 and CTLA-4 were expressed in female urethral carcinomas regardless of the histological subtype.

Conflict of interest

The authors declare no conflict of interest.

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