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Case Report

Systemic treatment for coexisting mucinous urethral adenocarcinoma and prostate adenocarcinoma

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Abbreviations & Acronyms
AE1/3 = cytokeratin AE1/AE3
CDX2 = caudal type homeobox 2
CEA = carcinoembryonic antigen
CK = cytokeratin
EGFR = epidermal growth factor receptor
EMT = epithelial-mesenchymal transition
FOLFIRI = folinic acid, 5-fluorouracil and irinotecan
MRI = magnetic resonance imaging
PSA = prostate-specific antigen

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Introduction: Mucinous urethral adenocarcinoma is a rare and progressive cancer of the prostatic urethra. Reports on palliative systemic treatment for mucinous urethral adenocarcinoma are few. We present a case of coexisting mucinous urethral and prostate adenocarcinomas managed with systemic treatment.

Case presentation: A 66-year-old man presented with gross hematuria and urinary retention. Prostate-specific antigen level was elevated, at 99 ng/mL, and prostate biopsy revealed moderately to poorly differentiated adenocarcinoma. Hormone therapy and standard chemotherapy for prostate adenocarcinoma were ineffective. Prostate re-biopsy revealed coexisting mucinous urethral and prostate adenocarcinomas. Gemcitabine + cisplatin chemotherapy and folinic acid + 5-fluorouracil + irinotecan chemotherapy temporarily suppressed the cancer, but 14 months after presentation, he developed liver metastasis and died. Autopsy revealed metastasis of both mucinous urethral adenocarcinoma and carcinosarcoma.

Conclusion: Mucinous urethral adenocarcinoma is difficult to diagnose in coexistence with prostate adenocarcinoma. This was an extremely rare case showing chemoresistance due to epithelial-mesenchymal transition.

Key words: adenocarcinoma, carcinosarcoma, epithelial-mesenchymal transition, prostate, urethral neoplasms.

Keynote message

In this case, appropriate systemic chemotherapy for mucinous urethral adenocarcinoma was delayed, and the disease progressed probably because of chemoresistance caused by EMT. The distinction between mucinous urethral adenocarcinoma and prostate adenocarcinoma may be difficult to identify because of histological similarities. Nevertheless, this distinction is crucial to treatment choice, and clinicians and pathologists should be aware of this rare cancer type.

Introduction

Mucinous urethral adenocarcinoma is an extremely rare and progressive cancer of the prostatic urethra. The initial symptoms are urinary retention and gross hematuria.[1] Urethroscopy may show space-occupying lesions in the prostatic urethra and T2-weighted MRI may show hyperintense signals in the prostate.[2] The prevalence of urethral adenocarcinoma in Europe is estimated at 0.1 per 1 million,[3] and only about 20 cases of mucinous urethral adenocarcinoma have been reported to date worldwide.[4] Because of its rarity, there are few reports of systemic treatment other than chemotherapy for mucinous urethral adenocarcinoma.

It is possible that more than one primary tumor may involve the prostate. The likelihood that a patient has multiple primary tumors is 2–17%.[5] Concurrent bladder cancer, colon cancer, or malignant melanoma is present in about 1% of prostate cancer cases during diagnosis.[6]

EMT is a phenomenon in which epithelial cells acquire mesenchymal traits. EMT increases the likelihood of cancer invasion and metastasis and increases resistance to chemotherapy.[7] EMT may be induced by cytotoxic chemotherapy.[8]

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Here, we report an extremely rare case of mucinous urethral adenocarcinoma coexisting with prostate adenocarcinoma, which was managed with systemic treatment.

Case presentation

A 66-year-old man was hospitalized for urinary retention and gross hematuria. Cystoscopy revealed a white lesion occupying the urethra (Fig. 1a), and blood sampling showed a high serum PSA concentration of 99 ng/mL. Imaging revealed gross irregularities in the prostate gland. Transrectal ultrasonography revealed a high-echo area surrounding the prostatic urethra, and T2-weighted MRI revealed an area with a non-uniform hyperintense signal around the prostate urethra. (Fig. 1a–c). Computed tomography showed para-aortic lymph node metastases (Fig. 2a). Transrectal prostate biopsy revealed an adenocarcinoma with a Gleason score of 4 + 5 in all 12 cores. Degarelix administration was started 2 weeks after admission for the treatment of metastatic prostate adenocarcinoma. Three months after admission, treatment with three courses of docetaxel and one course of cabazitaxel failed to inhibit the rapid increase in lymph node metastases despite low serum PSA levels (Fig. 2). Seven months after admission, para-aortic lymph node biopsy and prostate re-biopsy revealed enteric-type mucinous adenocarcinoma. Lymph node biopsies of the mucinous urethral adenocarcinoma showed negative results for microsatellite instability. Four courses of gemcitabine and cisplatin were administered, following which laboratory data showed a reduction in serum CEA concentration (Fig. 2). Eleven months after admission, three courses of FOLFIRI chemotherapy were administered because of progression of liver metastasis. FOLFIRI chemotherapy had a minimal effect, and dose reduction and treatment postponement were required because of grade 2 acute kidney injury and malaise according to Common Terminology Criteria for Adverse Events version 4. A course of gemcitabine–carboplatin combination therapy was administered 13 months after admission, but the patient died 1 month later because of liver metastasis. The patient and family consented to the autopsy and case report, and the autopsy was performed post-mortem.

Pathological features

The first prostate biopsy revealed PSA-negative and CEA-positive mucinous adenocarcinoma in 10% and PSA-positive and CEA-negative normal prostate adenocarcinoma in 90% of four cores around the urethra (Fig. 3a). A second prostate biopsy revealed a marked increase in the percentage of PSA-negative and CEA-positive mucinous adenocarcinomas (Fig. 3b). This mucinous adenocarcinoma had characteristics of an enteric-type adenocarcinoma, as shown by CK7 negativity, strong CK20 positivity, AE1/3 positivity, CDX2 positivity, and EGFR positivity (Fig. 3c). At autopsy, 90% of the prostate was found to be replaced by PSA-negative and CEA-positive mucinous adenocarcinomas. Metastases were found in the bladder, lungs, liver, pancreas, left kidney, left adrenal gland, lumbar spine, and peritoneum. However, most metastatic sites showed a mixture of mucin-producing adenocarcinoma and vimentin-positive carcinosarcoma (Fig. 3d,e).

Discussion

There are few reports on palliative systemic chemotherapy and no consensus on the systemic treatment for urethral adenocarcinoma. We chose cisplatin-gemcitabine and FOLFIRI

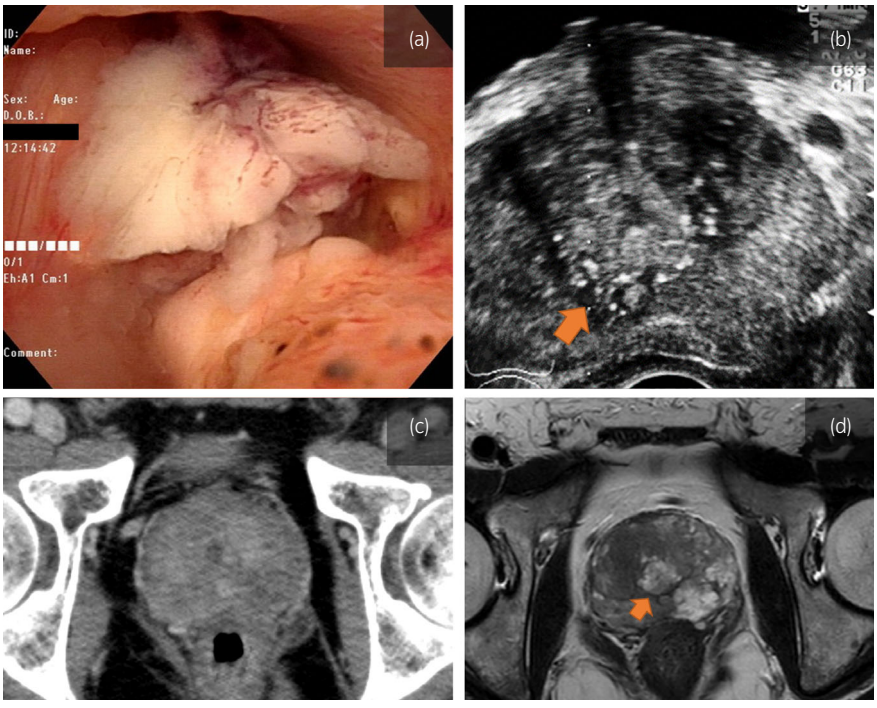


Fig. 1 (a) Cystoscopy showing a white tumor occupying the urethra. (b) Transrectal ultrasound at prostate biopsy showing a high-echo area around the urethra (arrow). (c) In contrast-enhanced computed tomography, the right lobe of the prostate is clearly contrast enhanced. Periurethral tumors are indistinguishable. (d) T2-weighted MRI showing an area with a non-uniform hyperintense signal around the prostate urethra (arrow) and an area with a hypointense signal predominantly in the right lobe of the prostate.

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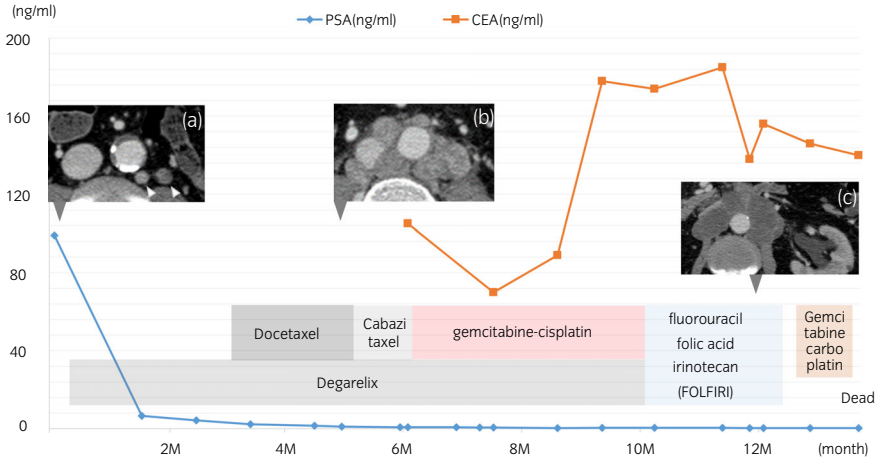


Fig. 2 Clinical course of prostate adenocarcinoma and mucinous urethral adenocarcinoma. (a) Contrast-enhanced computed tomography at the time of diagnosis showing para-aortic lymph node metastases. (b) Contrast-enhanced computed tomography after docetaxel showing an increase in para-aortic lymph nodes. (c) Contrast-enhanced computed tomography after two courses of FOLFIRI showing an enlargement of para-aortic lymph nodes and left hydronephrosis.

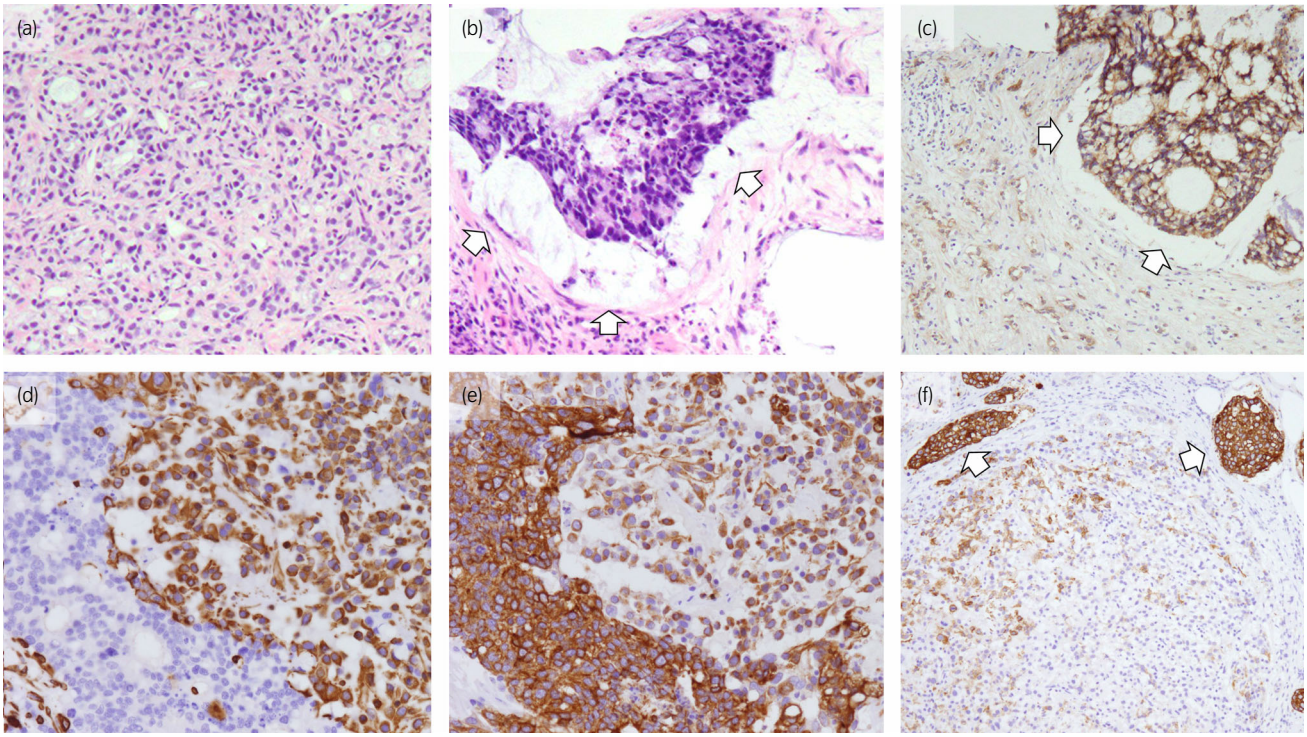


Fig. 3 (a) Hematoxylin and eosin staining for prostate at second prostate biopsy. Atypical cells show small tubular or cord-like structures. Prostate adenocarcinoma with a Gleason score of 4 + 5 was determined. This specimen is CEA-negative, PSA-positive, CK7-negative, and CK20-positive. (b) Hematoxylin and eosin staining for prostate at second prostate biopsy. Atypical epithelial cells show a cribriform pattern (arrow). Mucinous urethral adenocarcinoma was determined. The specimen is CEA-positive, PSA-negative, CK7-negative, CK20-positive, and CDX2-positive in enteric-like tissue with strong mucus production. (c) EGFR immunostaining for prostate at second prostate biopsy. The mucinous urethral adenocarcinoma specimen is EGFR-positive (arrow). The prostate adenocarcinoma specimen is weakly EGFR-positive. (d) Vimentin immunostaining for liver metastases at autopsy. The carcinosarcoma specimen is vimentin-positive, as seen in the upper right-hand corner of the figure. The mucinous urethral adenocarcinoma specimen is vimentin-negative, as seen in the lower left-hand corner of the figure. (e) AE1/3 immunostaining for liver metastases at autopsy. Part of the carcinosarcoma specimen is weakly AE1/3-positive, as seen in the upper right-hand corner of the figure. The mucinous urethral adenocarcinoma specimen is AE1/3-positive, as seen in the lower left-hand corner of the figure. (f) AE1/3 immunostaining for mesenteric lymph node metastases at autopsy. Most of the lymph vessels around the carcinosarcoma that had spread to the lymph nodes are infiltrated with AE1/3-positive adenocarcinoma (arrow).

therapy in this case. The treatment used for bladder adenocarcinoma is suitable for urethral adenocarcinoma because they have similar histopathological features.[9] Palliative systemic chemotherapy is effective for bladder adenocarcinoma, and a retrospective study has reported a progression-free survival of 10.6 months and overall survival of 24.5 months with chemotherapies consisting of 5-fluorouracil, cisplatin, and taxane.[10]

EMT may have played an important role in the progression and resistance of mucinous urethral adenocarcinoma in this case. It is believed that the mucinous urethral adenocarcinoma was converted to carcinosarcoma during lymphatic

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metastasis and invasion and became resistant to chemotherapies. Evidence for this is a part of the carcinosarcoma that showed AE1/3 positivity on immunostaining and that it had the same immunostaining characteristics as mucinous adenocarcinoma (Fig. 3e). In addition, AE1/3-positive adenocarcinoma was found in many lymphatic vessels near the carcinosarcoma of the primary and metastatic sites (Fig. 3f). Autopsy also revealed that carcinosarcomas predominated over mucinous urethral adenocarcinoma at most metastatic sites. Chemotherapies appear to have been successful for mucinous adenocarcinoma but not for carcinosarcoma.

We have considered other treatment modalities aside from chemotherapy. In this case, negative results for microsatellite instability were obtained, and immune checkpoint inhibitors were not indicated. In addition, immune checkpoint inhibitors may be ineffective in urethral adenocarcinoma because bladder adenocarcinoma has a low frequency of gene mutations and a low level of PD-L1 expression.[11] By contrast, EGFR inhibitors may be effective for mucinous urethral adenocarcinoma. Bryce *et al*.[4] reported a case in which multiple-gene panel testing revealed strong amplification and immunostaining of EGFR, contributing to successful treatment with erlotinib. In this case as well, EGFR immunostaining was strongly positive for mucinous urethral adenocarcinoma (Fig. 3c). We recommended multiple-gene panel testing for the administration of erlotinib; however, the patient refused testing because of financial and location-related issues.

Conclusion

It is important to distinguish mucinous urethral adenocarcinoma from other adenocarcinomas, such as prostate adenocarcinoma, mucinous prostate adenocarcinoma, and secondary cancer. In our rare case of coexisting mucinous urethral and prostate adenocarcinomas, difficulties in diagnosis and treatment arose from histopathological similarities. Thus, when there is a lesion adjacent to the urethra, pathologists should consider immunostaining for PSA, CEA, CK7, CK20, and CDX2 to detect prostate cancer, which is rare.[1] Liaison between the pathologist and the clinician could ensure early diagnosis in such cases. Finally, because no definitive conclusions can be drawn from this single case report, further studies based on case accumulation are warranted.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Editorial Comment

Editorial Comment to Systemic treatment for coexisting mucinous urethral adenocarcinoma and prostate adenocarcinoma

The coexistence of mucinous urethral and prostate adenocarcinoma is challenging to diagnose because of its rarity. Nezu *et al*. reported a case of coexisting mucinous urethral and prostate adenocarcinoma managed with systemic treatment.[1] They initially diagnosed a patient with prostate adenocarcinoma. However, hormone therapy and standard chemotherapy for prostate adenocarcinoma were ineffective. Re-biopsy showed mucinous adenocarcinoma, and they changed the hormone drug to a colon cancer regimen, followed by a bladder cancer regimen. Despite their best efforts, the patient died 14 months after clinical presentation. Autopsy implied that epithelial-mesenchymal transition had occurred in the metastatic lesions of the urethral adenocarcinoma.

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