Genomic analysis of bladder urothelial carcinoma with osteoclast-like giant cells: A case report

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Abstract. Urothelial carcinoma of the bladder with osteoclast-like giant cells (UCOGCs) is rare among the subtypes of poorly differentiated urothelial carcinoma. Its clinical significance and optimal treatment are unknown, and few reports on genomic analysis of UCOGCs have been reported. Detailed analysis including genetic analysis for rare type variants of cancer could be a foothold for further research. The present case describes the case of a 75-year-old man who presented with a non-papillary bladder tumor 56 mm in diameter showing gross hematuria and pain on voiding. Following transurethral resection of the bladder tumor, the pathological diagnosis was invasive UCOGCs. Neoadjuvant chemotherapy and radical cystectomy were performed with the resected tumor pathologically diagnosed as invasive UCOGCs, high grade, pT3b, pN1. The present study also analyzed the genomic features using a cancer panel test. The panel test noted six gene alterations (*PIK3CA* p.E542K, *HRAS* p.G13R, *ARAF* copy number amplification, *CDKN2A* copy number loss, *TP53* p.E285V, *ARID1A* p.S90Pfs*11) and telomerase reverse transcriptase (*TERT*) promoter variant. Accumulation of knowledge from molecular-based testing is anticipated to determine precise treatment for rare cancer.

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Abbreviations: OGC, osteoclast-like giant cell; UC, urothelial carcinoma; UCOGCs, urothelial carcinoma of the bladder with osteoclast-like giant cells; FFPE, formalin-fixed paraffin-embedded; CT, computed tomography; MRI, magnetic resonance imaging; TURBT, transurethral resection of the bladder tumor; CRP, C-reactive protein; TERT, telomerase reverse transcriptase

Key words: osteoclast-like giant cells, urothelial carcinoma with osteoclast-like giant cells, bladder cancer, rare subtype, gene alterations

Introduction

Although an osteoclast-like giant cell (OGC) tumor of bone is capable of malignancy, its typical feature is that of a benign tumor (1). OGC tumors in other organs, by contrast, are malignant neoplasms. OGC tumors have been found in several other organs including liver, breast, gallbladder, and pancreas (2-6). Among various histological subtypes of urothelial carcinoma (UC), carcinoma with OGC resembling a giant cell tumor of bone is extremely rare and only a few reports of urothelial carcinoma of the bladder with osteoclast-like giant cells (UCOGCs) have been reported (7-11). The fifth edition of the WHO Urinary and Male Genital Tumours classified UCOGCs as a poorly differentiated UC (12). The standard of care for and the prediction of the prognosis of UCOGCs remain unclear due to limited number of patients. To date, only one case report of UCOGCs with genetic testing has been reported. As the clinical utility of cancer gene panel testing in diagnosis and therapeutic decision-making is widely recognized, further accumulation of genomic results of UCOGCs is needed. Therefore, we performed genomic analysis of invasive UC with OGCs using a cancer panel test.

Case report

A 75-year-old man presented to Central Japan International Medical Center in November 2022 with gross hematuria and pain on voiding. Cystoscopy, computed tomography (CT), and magnetic resonance imaging (MRI) revealed a bladder tumor of 56 mm in diameter on the right wall of the bladder (Fig. 1A,B). Serum C-reactive protein (CRP) level was 10.19 mg/l. As no muscle invasion or metastasis was suspected, transurethral resection of the bladder tumor (TURBT) was performed (resected tumor weight: 54 g). Hematoxylin and eosin staining revealed that the tumor cells showed significant atypia and were accompanied by multinucleated cells positive for CD68

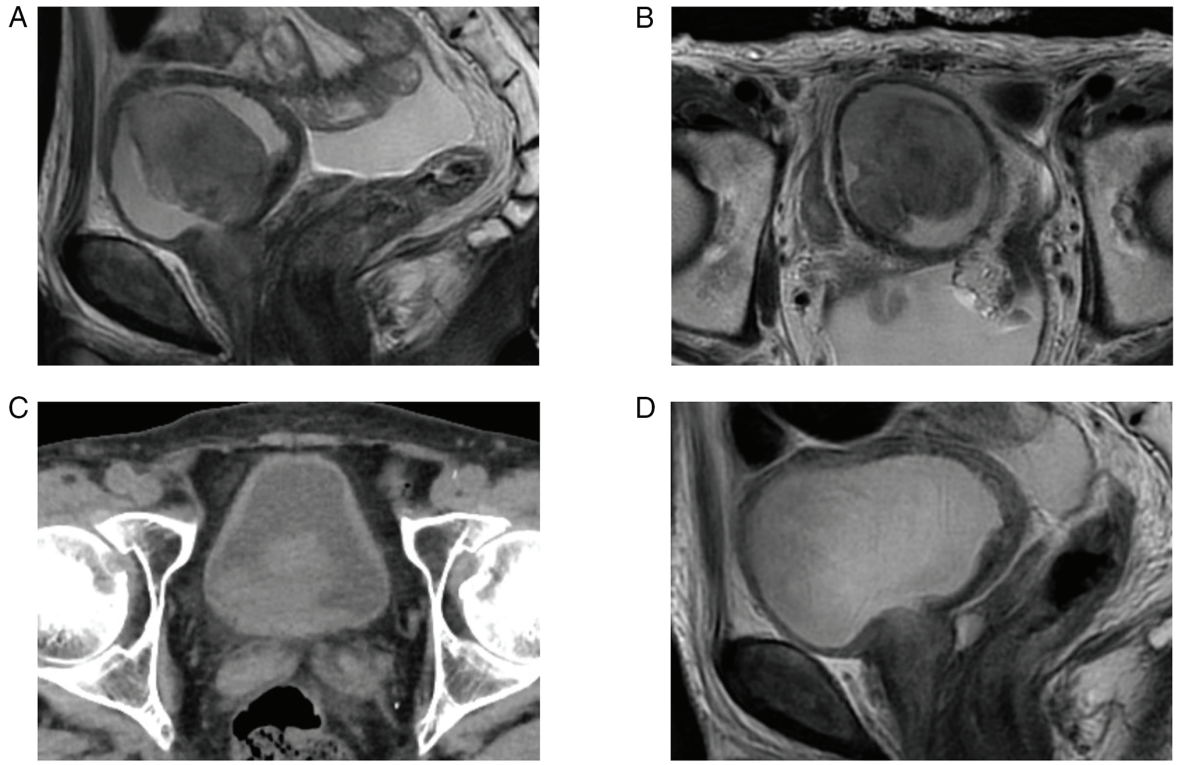

Figure 1. Images of bladder urothelial carcinoma with osteoclast-like giant cells. Pre-treatment MRI shows a large tumor from the right wall of the bladder: (A) Sagittal and (B) axial images. (C) Axial CT image after two courses of chemotherapy. (D) Sagittal MRI image after unplanned repeat TURBT was performed. CT, computed tomography; MRI, magnetic resonance imaging; TURBT, transurethral resection of the bladder tumor.

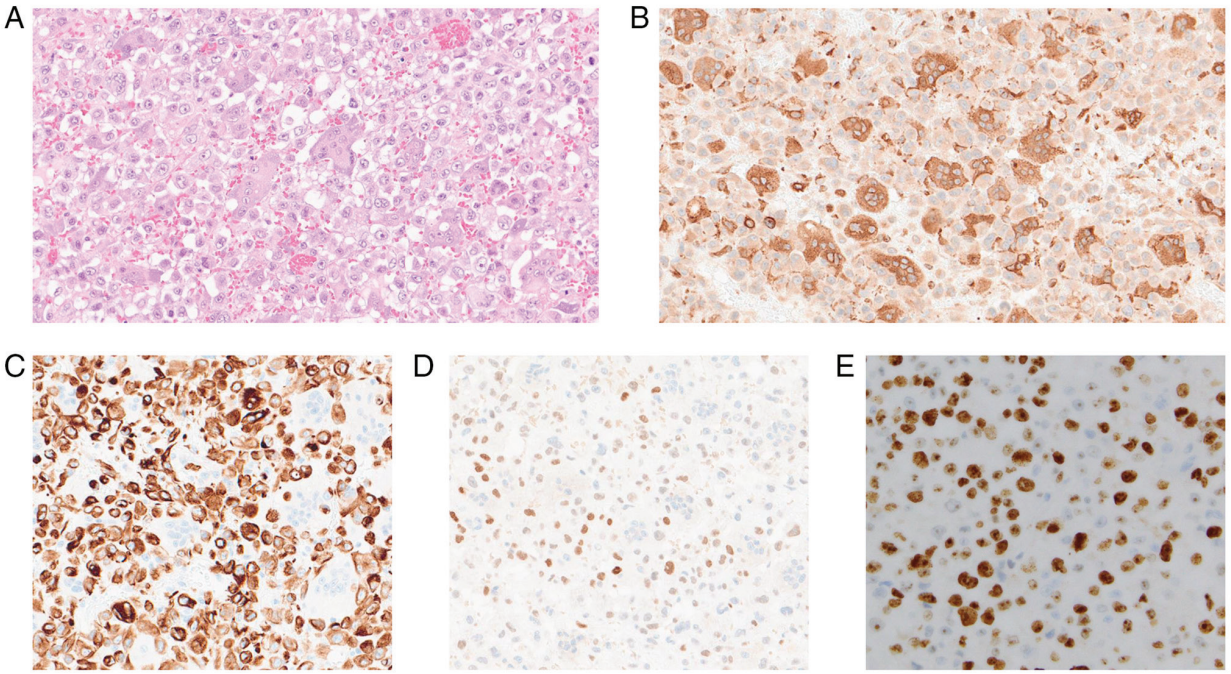

Figure 2. Microscopic findings of the tumor. (A) Hematoxylin and eosin staining shows OGC rich in the tumor (magnification, x200). (B) Immunohistochemistry shows that the multinuclear cells are CD68-positive (magnification, x200). Immunohistochemistry also shows the urothelial carcinoma to be (C) positive for AE1/AE3 except for the OGCs (magnification, x200), (D) partly positive for GATA3 (magnification, x200) and (E) strongly positive for Ki-67 (magnification, x400). OGC, osteoclast-like giant cell.

(Ventana Medical Systems, AZ, USA, 518-102425) (Fig. 2A,B). Immunohistochemistry also showed the tumor cells to be positive for AE1/AE3 (Ventana Medical Systems, 518-110178), partly positive for GATA3 (Ventana Medical Systems, 518-111953), and strongly positive for Ki-67 (Ventana Medical Systems, 518-102456) (Fig. 2C,D,E) but negative for CK7 (Ventana

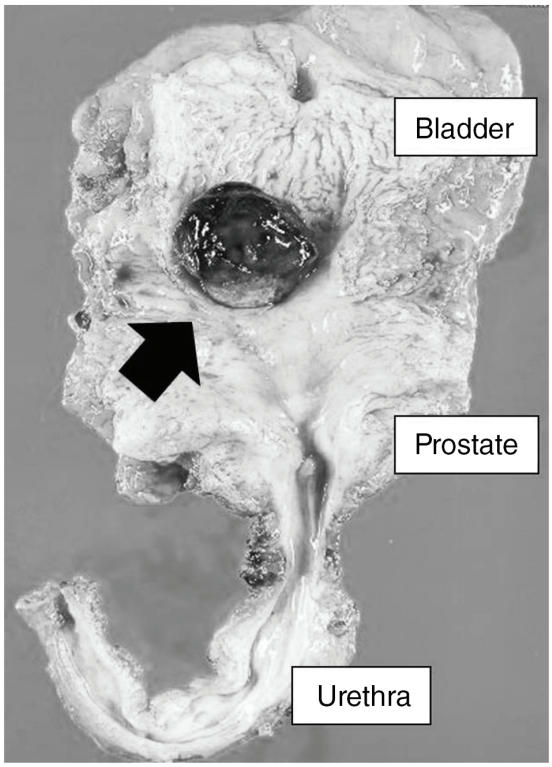

Figure 3. Macroscopic findings of the surgical specimen of the bladder with tumor (arrowhead).

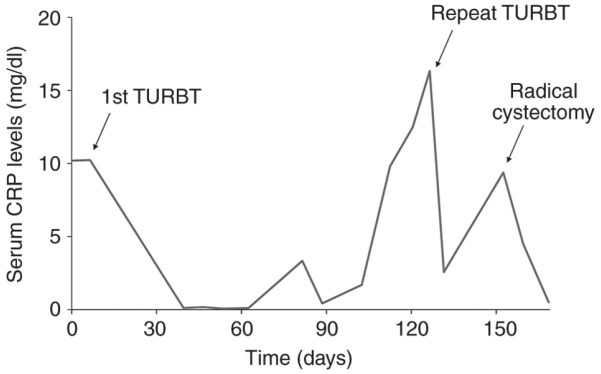

Figure 4. CRP levels during the clinical course. CRP, C-reactive protein; TURBT, transurethral resection of the bladder tumor.

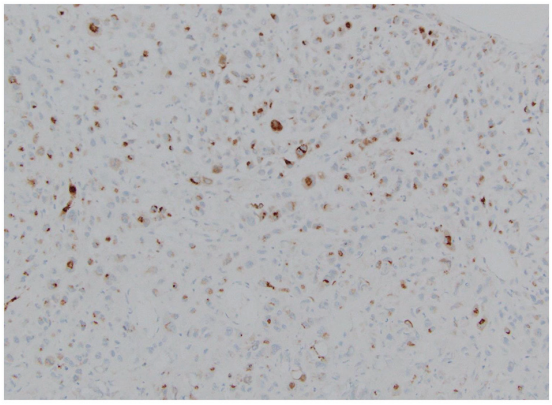

Figure 5. Immunohistochemistry shows tumor cells are positive for IL-6 (magnification, x200).

Medical Systems, 518-100902), CK20 (Ventana Medical Systems, 518-101152), CK5/6 (Ventana Medical Systems, 518-109851), and p63 (Ventana Medical Systems, 518-10961). Eventually, the tumor was pathologically diagnosed as UCOGCs with muscle invasion. As no standard of care for UCOGCs has been established, neoadjuvant chemotherapy using gemcitabine and cisplatin was started prior to radical cystectomy similar to treatment for usual muscle invasive cancer. A CT scan showed a large recurrent tumor in the bladder after the second course of chemotherapy (Fig. 1C), so radical cystectomy was planned rather than additional chemotherapy. During the surgical waiting time, at four months after the first TURBT, the patient suffered from pronounced bladder tamponade due to bleeding from the tumor, and he underwent unplanned repeat TURBT (resected tumor volume: 30 g). MRI just after surgery showed no residual tumor (Fig. 1D). One month later, robot-assisted radical cystectomy with lymph node dissection and ileal conduit reconstruction were performed. Macroscopically, a large recurrent tumor of 30 mm in diameter was observed again (Fig. 3), and pathological findings were invasive UC with OGCs, high grade, pT3b, pN1 (right internal iliac lymph node), RM0. Serum CRP levels were high when a high-volume tumor was present in the patient (Fig. 4). Additional immunohistochemistry showed tumor cells were positive for IL-6 (GeneTex, CA, USA, GTX110527) and OGCs were partly positive (Fig. 5).

Next, we analyzed the genomic features using a cancer panel test. The area containing predominantly tumor cells and OGCs was selected by a pathologist, and then the specimen was macro-dissected from formalin-fixed paraffin-embedded (FFPE) tissue sections. DNA isolation and sequencing following genome annotation and curation were performed as previously reported (13). Briefly, DNA was extracted using a Maxwell RSC DNA FFPE Kit-PKK, Custom (Promega, Fitchburg, WI, USA). DNA libraries were prepared for subsequent genomic sequencing following gene amplification using the GeneRead Human Comprehensive Cancer Panel (160 genes, NGHS-501X; Qiagen). Targeted amplicon exome sequencing for cancer-related genes was performed using the Illumina Miseq sequencing platform (Illumina, San Diego, CA, USA). Genome annotation and curation were performed using GenomeJack software (Mitsubishi Electric Software Corporation, Tokyo, Japan) (14). The genes detected with genetic alterations were as follows: *TERT* promoter (-124C>T; ClinVar pathogenic), *PIK3CA* (E542K; ClinVar pathogenic), *HRAS* (G13R; ClinVar pathogenic), *ARAF* (5 times the copy number amplification), *CDKN2A* (copy number loss), *TP53* (E285V; ClinVar pathogenic), and *ARID1A* (truncate mutation). Tumor mutation burden was 5.9 Mut/Mbp, and microsatellite instability status was stable.

Discussion

Various pathological subtypes of UC are known. Among them, UCOGCs is included in the subtype of poorly differentiated UC (12). Its clinical symptoms are similar to those of conventional UC (e.g., gross hematuria) (7-11) and our patient presented with hematuria and pain on voiding. The clinical characteristics of the rare subtypes of UC are poorly understood, and no standard or optimal treatment has been established due to the limited number of cases (15). In previous reports,

surgical treatment of either TURBT or radical cystectomy was performed for invasive UC with OGC of the bladder (7-11). In those cases, both no recurrence of cancer and an aggressive clinical course with patient deaths were reported. Several subtypes of UC have been reported as predictive factors for worse clinical outcomes (16,17). Our patient showed no recurrence during the 10 months after the surgery without adjuvant chemotherapy, but the postoperative follow-up period was too short to evaluate recurrence adequately.

UCOGCs is usually composed of mononuclear carcinoma cells, host histiocytes, and multinucleated OGCs. A conventional component of UC often coexists with UCOGCs (12). As shown in our result, OGCs show no nuclear pleomorphism of the nuclei, and they are positive for CD68 histiocytic markers (12,18).

There are many reports on the relationship between serum CRP levels and various cancers including bladder cancer (19,20). The preoperative CRP levels were reported to be a predictive factor for primary tumor stage, lymph node metastasis, and cancer-specific and overall survival in muscle invasive bladder cancer (20). In the present case, CRP levels were high when tumor volumes were high. We previously reported that prostate cancer cell lines secrete IL-6 and IL-8 and that those chemokines promote CD11b-positive cells to differentiate into osteoclast like multinuclear cells (21). We infer that IL-6 secreted from tumor cells may promote OGC formation and increase CRP levels in our case.

As UCOGCs is a very rare subtype of UC, few genomic studies have been reported. To the best of our knowledge, only a single case of genomic testing for UCOGCs has been reported, and it showed a *TP53* mutation (11). UC had a higher rate of genomic alteration compared to that of other urologic cancers (13). In the present case, we found pathogenic variants in five genes including *TP53* and copy number alterations in two genes. These genomic alterations were similar to those in conventional urothelial carcinomas (22-26). To explain the difference in clinical course between UCOGCs and conventional UC, further research including whole genome sequencing will be needed.

There are several reports on genomic analysis of OGCs other than UC. Mutations in *KRAS*, *BRCA2*, *CDKN2A*, *TP53*, *SMAD4*, and *GNAS* in undifferentiated carcinoma with OGCs of the pancreas are reported (27-29). A mutation in *TP53* was identified in uterine leiomyosarcoma with OGCs (30). It was also reported that genetic testing has been linked to treatment for undifferentiated carcinoma with OGCs of the pancreas. Although pancreatic cancers generally exhibit a suboptimal response to immune checkpoint inhibitors, pembrolizumab as a third-line therapy is more effective for pancreatic cancers of undifferentiated carcinoma with OGCs showing a high tumor mutation burden (31). Platinum-based chemotherapy is standard treatment for advanced bladder cancer (32-34). Mutations in *ARID1A*, *TP53*, and *MDM2* were reported as negative predictive factors for platinum-based chemotherapy (35-38). In our case, it is possible that some genetic mutation is responsible for platinum-based drug resistance. Therefore, targeted therapy based on the result of genomic test could be considered in next treatment.

In conclusion, we showed genomic alteration in a patient with UCOGCs. Genetic alterations or IL-6 production may be associated with increased inflammatory response and OGC formation, as well as resistance to cisplatin-based chemotherapy. These results may contribute to further research on UCOGCs to find precise treatments for this rare disease.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KK and KMi conceived the study. KK, KMi, TY, SS, KMa, KH, YK, HN, SI and TD contributed to data analysis and interpretation. KK, KMi, SK and SY performed clinical evaluations and treatment. KK and KMi wrote and edited the manuscript. KK and KMi confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent participate

This study was approved by the research ethics committee of Central Japan International Medical Center (approval no. 2022-013). Written informed consent was obtained from the patient for this study.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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