Introduction: Urothelial neoplasms with a varus growth pattern are rare, and few urologists have encountered inverted urothelial carcinoma of the ureter.

Case presentation: An 82-year-old man was referred to our hospital for investigation of gross hematuria. Magnetic resonance imaging revealed nodules measuring 1–2 mm in diameter in the left upper ureter with slight reduction in signal intensity on diffusion-weighted imaging. Ureteroscopy showed a pedunculated smooth tumor that had the appearance of an inverted papilloma rather than the papillary shape typical of urothelial carcinoma. The tumor was biopsied and histopathological examination revealed a noninvasive, low-grade urothelial carcinoma with inverted multiple layers. Laparoscopic radical nephroureterectomy was subsequently performed, and a pedunculated tumor measuring 20 mm in diameter was found in the left upper ureter. The histopathological diagnosis was inverted papillary urothelial carcinoma, low-grade, pTa, pN0.

Conclusion: This report provides the first clinical description of inverted papillary urothelial carcinoma of the ureter.

Key words: inverted papilloma, ureteral neoplasms, ureteroscopy, urologic neoplasms, urothelial carcinoma.

Keynote message
Urothelial neoplasms with a varus growth pattern are rare, especially in the ureter. This report describes a case of inverted urothelial carcinoma of the ureter that had the appearance of a smooth nodule-like inverted papilloma and was difficult to diagnose. Urologists should be aware of urothelial neoplasms with a varus growth pattern. Inverted urothelial carcinoma is distinct from inverted papilloma in terms of its biological behavior and requires a different treatment strategy.

Introduction
Most urothelial neoplasms present with a papillary growth pattern, and tumors with a varus growth pattern are rare.1 IP, which is a benign lesion, was included in the 2004 WHO classification of bladder tumors.2 However, malignant inverted tumors are not yet categorized in the recently revised 2016 WHO classification.3 Therefore, most urologists would be unaware of inverted urothelial carcinoma. In 2015, the ICUD Consensus Conference recommended that urothelial tumors showing varus growth be classified according to the degree of nuclear atypia in the WHO and International Society of Urological Pathology classification.4 This report is the first to describe the clinical findings in a case of inverted papillary urothelial carcinoma of the ureter.

Case presentation
An 82-year-old man was referred to our hospital with gross hematuria. Flexible cystoscopy revealed slight hematuria from the left ureteral orifice but there was no suspicion of a bladder tumor. There were no abnormal findings on abdominal ultrasonography or plain computed tomography scans. Magnetic resonance imaging revealed nodules measuring 1–2 mm in...
diameter in the left upper ureter with slight reduction in signal intensity on diffusion-weighted images (Fig. 1). Urine cytology was negative.

Ureteroscopy and retrograde pyelography under general anesthesia revealed a tumor in the left upper ureter (Fig. 2). The smooth-edged, pedunculated, and nodular appearance of the tumor suggested IP rather than urothelial carcinoma, which typically has a papillary shape. Multiple small nodules were found around the tumor. Biopsy specimens were taken from both the main tumor and the nodules. Histologically, the surface of the neoplasm was covered with non-neoplastic urothelium containing umbrella cells. The tumor had a varus growth pattern and contained moderate to large irregular trabeculae. Mild to moderate cytologic atypia and loss of polarity were apparent in high-power views. Histopathological examination demonstrated noninvasive, low-grade urothelial carcinoma with multiple inverted layers (Fig. 3). There was no apparent tumor in the ureter downstream or in the bladder. Urinary histology for the left upper ureter was negative. Laparoscopic radical nephroureterectomy was performed, and a pedunculated tumor measuring 20 mm in diameter was detected in the left upper ureter. The tumor had a varus growth pattern but had not invaded the lamina propria. The histopathological diagnosis was inverted papillary urothelial carcinoma, low-grade, pTa, pN0 (Fig. 4). There have been no signs of recurrence as of 6 months after surgery.

**Discussion**

Inverted urothelial carcinoma is a rare bladder tumor that was first described in 1997 by Amin et al. Although a few case reports have been published since then, this entity is not yet categorized in the WHO classification of bladder tumors. In 2015, the ICUD recommended that urothelial tumors with a varus growth pattern be classified into five categories: (i) IP; (ii) inverted papillary urothelial neoplasm of low malignant potential; (iii) IPUC, low-grade, noninvasive; (iv) IPUC, high-grade, noninvasive; and (v) IPUC, high-grade, invasive.

Unlike urothelial carcinoma, IP does not warrant frequent long-term follow-up because it is considered to be a benign tumor and not a risk factor for the occurrence of urothelial carcinoma. However, the risk of invasiveness and recurrence of IPUC is estimated to be similar to that of exophytic papillary cancer. Despite the difficulty in distinguishing between IP and IPUC histologically, the distinction is important because the biologic behavior of these entities is very different, as is their treatment. There have been cases of urothelial neoplasms with an inverted growth pattern that were recently diagnosed as inverted urothelial carcinoma. IPUC shows substantial nuclear pleomorphism, readily apparent mitotic figures, and architectural abnormalities consistent with urothelial carcinoma.

In this case, the tumor had a smooth edge and appeared to be covered in normal mucosa. IP was suspected from the shape of the tumor. However, inverted urothelial carcinoma was detected by histopathologic analysis (Fig. 3). Immunohistochemical expression of Ki-67 expression is reported to be high in urothelial carcinoma with a varus growth pattern. Jones et al. reported that Ki-67 was highly expressed in urothelial carcinoma with a varus growth pattern, and that Ki-67 was not expressed in IP. In this case, high expression of Ki-67 was observed in the tumor part and low in the non-tumor part (Fig. 4f), and it was diagnosed as IPUC rather
than IP. Accurate pathological diagnosis of malignancy allowed appropriate surgical intervention. Minimally invasive surgery such as renal preservation or partial resection was also considered for old age and low malignancy, but the patient himself selected laparoscopic radical nephroureterectomy because of the atypical histopathology. Pathological examination confirmed complete resection of the tumor and there have been no signs of recurrence as of 6 months after surgery.

Contrary to our expectation that the neoplasm detected in this case would be IP, the histopathological findings were of IPUC, which is unfamiliar to most urologists. Sometimes a ureteroscopic biopsy does not give an accurate diagnosis, but in the upper urinary tract, a seemingly benign tumor may be malignant. Histopathological findings as well as endoscopic findings are important, and diagnosis must be made carefully.

**Conclusion**

Both urologists and pathologists should be aware that urothelial neoplasms other than IP may also have a varus growth pattern.

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**Fig. 3** Histological findings of the biopsy specimen. (a) At low magnification, a urothelial nest is seen exhibiting endophytic growth in the lamina propria (arrows) and covered with non-neoplastic epithelium with umbrella cells (arrow heads). This urothelial nest (arrows) has multiple layers and a smooth basement membrane. (b) At high magnification, the tumor shows mild to moderate cytological atypia and loss of polarity consistent with low-grade urothelial carcinoma. (c) The tumor was covered by a non-neoplastic epithelium with umbrella cells (arrows).

**Fig. 4** Histological findings of the surgical specimen. (a) Under loupe magnification, the tumor is nodular in shape with a smooth edge. (b) The tumor shows large trabeculae of varying sizes with an inverted growth pattern. The surface of the tumor is covered with non-neoplastic epithelium. (c) The stromal–epithelial interface is smooth without stromal reaction or micronests. These findings suggest that the tumor has not invaded the lamina propria. (d) At high magnification, the tumor shows mild to moderate cytological and architectural disorder. (e) The tumor was covered by a non-neoplastic epithelium with umbrella cells (arrows). (f) High immunohistochemical expression of Ki-67 was observed only in the tumorous part.
Author Contribution

Takuma Nirei: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing. Noboru Nakaigawa: Project administration; Writing – review & editing. Mai Matsumura: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing. Toshiaki Kataoka: Data curation; Investigation. Takahiro Nagasaka: Data curation. Kota Aomori: Data curation. Yusuke Ito: Data curation. Kentaro Muraoka: Data curation. Masahiro Yao: Supervision.

Conflict of interest

Not applicable. The authors declare no conflicts of interest.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

All informed consent was obtained from the subject.

Registry and the registration no. of the study/trial

Not applicable.

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