Tubulovillous adenoma with high-grade dysplasia of the vulva harboring high tumor mutational burden and cancer-associated mutations: a case report

Hanako Sato1, Kosuke Murakami1,*, Tomoyuki Otani1,2 and Noriomi Matsumura1

Abstract

Background: Vulvar cancer is a rare disease, accounting for approximately 5% of gynecological malignancies. Primary adenocarcinoma of intestinal-type of the vulva or its precancerous lesion is extremely rare, and details regarding its origin, evolution and related genetic mutations are unknown. Treatment options for this cancer have not been defined.

Case presentation: A 63-year-old Japanese woman came to the hospital because she was aware of a vulvar mass. There was a 1 cm mass on the dorsal side of the vulva, just outside the remains of the hymen. Biopsy revealed suspected adenocarcinoma, and wide local excision was performed. From histopathology and immunohistochemistry, the specimen was diagnosed as tubulovillous adenoma with high-grade dysplasia of the vulva. No other primary lesions were found, and the vulva was considered the primary site. A gene panel test (FoundationOneCDx assay) showed a high tumor mutational burden and mutations in TP53, KEL, RB1, RNF43, PTEN, GNAS, and PIK3CA.

Conclusions: The current case of tubulovillous adenoma with high-grade dysplasia of the vulva had a variety of cancer-associated mutations, despite being a precancerous lesion. In cases of intestinal-type neoplasms of the vulva, it may be helpful to check tumor mutational burden and gene mutations for treatment selection.

Keywords: Adenocarcinoma of intestinal-type, Tumor mutational burden, Tubulovillous adenoma, Vagina, Vulva, Vulvar cancer

Background

Vulvar cancer accounts for only approximately 3–4% of gynecologic malignancies [1]. Approximately 80% of vulvar cancers are squamous cell carcinoma, followed by basal cell carcinoma, Paget’s disease, and melanoma; adenocarcinoma is very rare [1]. Adenocarcinoma of intestinal-type of the vulva was first reported in 1964 [2] and is diagnosed based on characteristic pathologic findings and immunohistochemistry (IHC).

Several theories have been reported regarding the origin of intestinal-type neoplasms of the vulva: the urethra, lower vaginal area, and rectum are derived from the cloaca, so the lower vaginal area contains remnants of bowel tissue [3]; ectopic bowel epithelium or intestinal metaplasia within the tissue derived from Müllerian duct [4]; and Bartholin’s glands in the vulva [5]. The precise origin and the evolution of intestinal-type neoplasms of the vulva remain unknown and there is no established treatment. Additionally, the genetic mutation patterns of intestinal-type neoplasms of the vulva have not been investigated.
Here, we report a case of tubulovillous adenoma with high-grade dysplasia of the vulva, as a precancerous lesion of intestinal-type neoplasm of the vulva, with multiple cancer-associated mutations and high tumor mutational burden (TMB).

**Case presentation**

A 63-year-old Japanese woman, gravida 4, para 3, was aware of a mass in the vulva and visited the clinic. She has no medical or family history and no smoking history. There was a 1 cm mass on the vulva that had self-destructed. Biopsy revealed a dysplastic glandular neoplasm (Fig. 1A), and the histopathological diagnosis was adenocarcinoma. The pathological findings were not typical for vulvar primary cancer, and metastatic carcinoma of gastrointestinal origin was suspected. The patient was referred to our hospital.

Gross findings at the time of the visit to our hospital were redness with ulceration of approximately 5 mm just outside the 7 o’clock remains of the hymen, and the mass had disappeared (Fig. 1B). On magnetic resonance imaging, no obvious mass was detected on both T1-weighted and T2-weighted images, but on the diffusion-weighted image, there was a high-signal area of approximately 5 mm that was presumed to be a tumor lesion (Fig. 1C, D). Contrast-enhanced computed tomography and positron emission tomography showed no enlarged lymph nodes or distant metastases.

---

**Fig. 1** MRI and visual findings (after biopsy). A Hematoxylin–eosin staining of the biopsy specimen. Magnification: 100 x, scale bar: 250 µm. B Visual findings. There was a red lesion at the vaginal entry at 7 o’clock (black arrowhead). C MRI T2-weighted image (axial). The lesion showed a high signal (white arrowhead). D MRI diffusion-weighted image (axial). The lesion showed restricted diffusion (white arrowhead). E Surgical specimen. The thread indicates the ventral direction.
Tumor markers were as follows: CEA, 1.8 ng/mL; CA125, 12 U/mL; and CA19-9, 40 U/mL. Only CA19-9 was slightly elevated. Upper gastrointestinal endoscopy revealed erosions in the gastric angulus, from which one biopsy was performed, but no malignant findings were observed. Lower gastrointestinal endoscopy revealed no abnormal findings. Wide local excision of the vulvar tumor was performed under spinal anesthesia. The resected specimen was $2 \times 1 \times 1$ cm in size with a margin at the site of the probable tumor (Fig. 1E). Grossly, there was an approximate 5 mm depression in the skin. The operation took 23 min and there was minimal blood loss. The postoperative course was good, and the patient was discharged the day after surgery.

Histologic examination revealed that the tumor was situated in the mucosa covered by squamous epithelium, some portion of which had sebaceous glands. The tumor was a cystic lesion invaginating from the surface and was lined by a tubulovillous proliferation of dysplastic columnar epithelium (Fig. 2A). The nuclei were enlarged, and nucleoli were prominent. The mitotic activity was brisk. There were some fused glands, which were especially apparent in the tissue obtained in biopsy (Fig. 1A). Some dysplastic glands were on the mucosal surface and continuous with the non-neoplastic squamous epithelium (Fig. 2A, B). The tumor was well-circumscribed, with no infiltrative growth or lymphovascular infiltration. Sebaceous glands were the only non-dysplastic glandular elements present in the vicinity of the tumor; Skene glands, minor vestibular glands, endometriosis, ectopic intestinal mucosa, and intestinal metaplasia were not identified. A portion of Bartholin gland was in the periphery of the resected specimen, apart from the tumor.

IHC results were as follows: cytokeratin (CK) 20: positive, CK7: focal positive, CDX2: positive, estrogen receptor (ER): negative, progestosterone receptor (PgR): negative, and PAX8: negative (Fig. 3A–F). p16 expression was strong and diffusely positive (Fig. 3G), and human papillomavirus (HPV) was negative (Fig. 3H). p53 was null pattern (Fig. 3I). P532 and MSH6 expressions were detected (Fig. 3 J, K). On the basis of these results, the patient was diagnosed with primary adenocarcinoma of intestinal-type of the vulva. A gene panel test (FoundationOneCDx assay, Foundation Medicine, Inc., Cambridge, MA, USA) was performed on the tumor portion of the explanted specimen. TMB was high, at 13 mutations/megabase (Mut/Mb). The tumor was microsatellite stable. Gene mutations in TP53, KEL, RB1, RNF43, PTEN, GNAS, and PIK3CA were detected (Table 1).

The patient did not receive any adjuvant therapy. At 30 months postoperation, there has been no recurrence.

![Fig. 2 Pathological findings of hematoxylin–eosin staining. A Hematoxylin–eosin staining. A magnified view of the arrowhead is shown in (B). The asterisk indicates contamination. Magnification: 12.5 x, scale bar: 1000 µm. B Magnified view of the arrowhead in (A). Magnification: 100 x, scale bar: 100 µm](image)

**Discussion and conclusions**

Thirty cases of adenocarcinoma of intestinal-type of the vulva or vagina have been reported. The cases were reported in a wide range of countries and races, and the mean patient age is 54.1 (31–69) years (Table 2) [3–30]. Symptoms of adenocarcinoma of intestinal-type of the vulva include pain, itching, and bleeding. In the early stage of cancer or precancerous lesion, as in the present case, the patient may present only with a mass (Table 2). One report suggests that adenocarcinoma of intestinal-type of the vulva may have a poor prognosis and that endoscopic follow-up of the colon is mandatory because of the high tendency to complicate gastrointestinal tumors [18]. In most cases, however, the clinical courses are gradual, and the prognosis is good (Table 2).

Intestinal-type neoplasms of the vagina were reported to be like the adenoma-carcinoma sequence in colorectal tumors [31]. However, intestinal-type neoplasms of the vulva are rarer, and the adenoma-adenocarcinoma sequence has not been discussed. There are no reports of genetic analysis of intestinal-type adenomas of the vulva, and there have been only few reports of genetic analysis of adenocarcinoma of intestinal-type of the...
vulva or intestinal-type adenomas/adenocarcinomas of the vagina. In the current case, which was a precancerous lesion diagnosed as tubulovillous adenoma with high-grade dysplasia of the vulva, genetic analysis was performed and high TMB was detected, accompanied by many cancer-associated gene mutations. This lesion may be in the process of carcinogenesis, and the genetic mutations may be related to malignant transformation.

In the context of histopathological diagnosis considering tumor evolution, this case is very important. Adenocarcinoma of intestinal-type of the vulva resembles colorectal villous adenoma [32]. However, adenoma of intestinal-type of the vulva as a non-invasive, precancerous lesion has not been clearly defined. The tumor in the current case is an epithelial tumor with intestinal traits; following the classification of colorectal tumors, the most similar histomorphology is tubulovillous adenoma with high-grade dysplasia. Conventional colorectal adenoma recapitulates the normal crypt architecture of the mucosa in typical and early stage lesions, while some lesions also develop a villiform architecture. In the WHO classification, conventional colorectal adenoma is divided into tubular adenoma, tubulovillous adenoma, and villous adenoma depending on the ratio of tubular to villous structures [33]. Conventional colorectal adenoma is further divided into tumors with low-grade dysplasia and high-grade dysplasia [33]. Based on the context of colorectal adenoma, this case was diagnosed as tubulovillous adenoma with high-grade dysplasia. Fox et al. first reported a vaginal intestinal-type adenoma in 1988 [6]. Vitrey et al. reported low-grade adenoma of the vulva in 2003 [34]. In 2012, Karakouch et al. reported multiple tubulovillous adenomas of the vulva, including adenocarcinoma [19]. However, our report is the first case of tubulovillous adenoma with high-grade dysplasia that is expansile in the direction of the mucosa. We reviewed previous reports of adenocarcinoma of intestinal-type of the vulva, and the report by Willén et al. is likely a villous adenoma with an uncertain degree of dysplasia in the context of a colorectal adenoma [10]. Matsuzaki et al. reported villoglandular adenocarcinoma of the vulva without stromal invasion [24], which could also be considered tubulovillous adenoma with high-grade dysplasia. The
Table 2  Cases of intestinal-type adenocarcinoma of vulva and vagina

| Year | First Author | Country | Race | Age | Symptom | Location | Maximum tumor size (cm) | Operation | Adjuvant therapy | Stage | LN meta | Follow (month) | Prognosis | CK20 | CK7 | CEA | CDX2 | p16 | ER | PR |
|------|--------------|---------|------|-----|---------|----------|-------------------------|-----------|-------------------|-------|---------|--------------|-----------|------|-----|-----|------|-----|----|----|
| 1978 | Tiltman      | South Africa | NA   | 50  | dyspareunia, discharge | external urethral meatus, left lateral and anterior vaginal wall | 2          | RV+LND         | none | II     | positive 12 | NED       | NA   | NA  | -   | NA   | NA  | NA | NA |
| 1988 | Fox          | UK      | NA   | 35  | discharge, bleeding   | posterior rim of hymenal caruncle | 1.7        | WLE               | none | NA     | NA 27       | rec 23 m re-section | NA   | NA  | +   | NA   | NA  | NA | NA |
| 1991 | Mortensen    | Denmark | NA   | 43  | discharge, bleeding   | frenulum of labia minor | 1.5        | WLE               | none | I      | negative 48 | NED       | NA   | NA  | NA  | NA   | NA  | NA | NA |
| 1993 | Kennedy      | USA     | NA   | 54  | vulvar mass           | frenulum of labia minor | 1.7        | RV+LND           | none | I      | negative 17 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 1993 | Kennedy      | USA     | NA   | 63  | None                  | anterior-lateral upper vaginal wall | NA         | WLE               | NA    | NA     | NA 26       | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 1999 | Nagar        | UK      | NA   | 36  | bleeding              | posterior vestibule | 1          | WLE               | none | I      | negative 12 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 1999 | Willen       | Sweden  | NA   | 57  | None                  | left posterior vestibule | 1          | WLE               | none | I      | negative 18 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 2001 | Mudhar       | UK      | NA   | 56  | bleeding, discharge   | posterior vaginal wall | 1          | WLE               | none | I      | negative 12 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 2001 | Zaidi        | USA     | African | 43 | vulvar mass, discomfort, bleeding | frenulum of labia minor | 1.5        | RV+LND           | none | NA     | negative 18 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 2001 | Rodriguez     | Spain   | NA   | 69  | None                  | right labia major | 1.5        | WLE               | none | I      | negative 36 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 2003 | Liu          | Taiwan  | Asian | 49  | NA                  | left labia major | 2          | RV+LND           | none | I      | negative 24 | NED       | NA   | NA  | NA  | NA   | NA  | NA | NA |
| 2004 | Dube         | Canada  | NA   | 58  | vulvar mass, discomfort, burning | frenulum of labia minor | 1.5        | RV                | none | I      | negative 16 | NED       | NA   | NA  | +   | NA   | NA  | NA | NA |
| 2005 | Lee          | Korea   | Asian | 61  | spotting vaginal introitus (11 o'clock) | 2          | WLE+laser       | none | I      | negative 9 | rec 9 m:WLE | +   | NA | NA  | NA   | NA  | NA | NA |
| Year | First Author | Country  | Race  | Age  | Symptom | Location                                      | Maximum tumor size (cm) | Operation | Adjuvant therapy | Stage | LN meta | Follow (month) | Prognosis | CK20 | CK7 | CEA | CDX2 | p16 | ER | PR |
|------|--------------|----------|-------|------|---------|-----------------------------------------------|-------------------------|-----------|------------------|-------|---------|---------------|-----------|------|-----|-----|-----|-----|----|----|
| 2006 | Tjalma       | Belgium  | NA    | 55   | bleeding| posterior and anterior lower vaginal wall     | 4.5                     | PE        | none             | II    | negative| 20            | NED       | +    | +   | NA  | NA  | NA  |    |    |
| 2012 | Cormio       | Italy    | NA    | 59   | discomfort, burning| left posterior vestibule | NA                     | RV + LND  | chemo            | NA    | NA      | 54            | DOD       | +    | +   | NA  | NA  | NA  |    |    |
| 2012 | Cormio       | Italy    | NA    | 42   | none    | vulva                                          | 1                       | RV + LND  | none             | NA    | NA      | 39            | NED       | +    | +   | NA  | NA  | NA  |    |    |
| 2012 | Karkouche    | France   | Caucasian | 31   | none    | bilateral labia minor                          | 1.3                     | WLE       | none             | NA    | NA      | 15            | NED       | +    | -   | NA  | NA  | NA  |    |    |
| 2013 | Wessel       | Belgium  | Caucasian | 68   | discharge, vulvar mass, pain | posterior vaginal introitus right labia major | 5                       | RV + LND  | neoadjuvant chemo (PTX + CDDP) | III   | positive| 4             | NED       | -    | +   | +   | +   | -   | NA |
| 2016 | Sui          | China    | Asian  | 43   | vulvar mass, bleeding | vulvar mass, itching | 1.3                     | WLE       | chemo (PTX + CBDCA) | I     | negative| 24            | NED       | -    | +   | NA  | NA  | +   | -  |    |
| 2016 | Tepeoglu     | Turkey   | NA    | 40   | vulvar discomfort, bleeding | left labia minor | 2                       | WLE + LND | none             | III   | positive| 38            | NED       | +    | +   | +   | +   | NA  | NA |
| 2017 | Matsuzaki    | Japan    | Asian  | 68   | vulvar mass | vestibule | 4                       | WLE       | none             | in situ| negative| 60            | NED       | +    | -   | NA  | NA  | NA  |    |    |
| 2017 | Lee          | Korea    | Asian  | 64   | vulvar mass, itching | vulvar mass | 4                       | WLE       | none             | II    | negative| 12            | NED       | +    | +   | +   | +   | +   | NA |
| 2017 | He           | China    | NA    | 63   | vulvar mass | frenulum of labia minor vestibule | 2                       | WLE       | none             | NA    | NA      | 26            | NED       | +    | +   | +   | +   | -   | -  |    |
| 2019 | Kurita       | Japan    | Asian  | 63   | bleeding | vestibule | 2                       | WLE + LND | RT               | I     | negative| 12            | NED       | +    | -   | NA  | NA  | NA  |    |    |
| 2019 | Kaltenecker  | USA      | African | 53   | vulvar mass, itching, pain, discharge | bilateral labia minor | 6                       | WLE       | chemo (PTX + CBDCA + RT) | IV    | positive| 12            | DOO       | +    | -   | NA  | NA  | NA  |    |    |
| 2019 | Ugwu         | Nigeria  | African | 40   | vulvar mass, bleeding, pain | posterior lower vaginal wall left labia minor | 6                       | WLE       | CCRT             | I     | negative| NA            | NED       | NA   | NA  | NA  | NA  | NA  |    |    |
| 2022 | Moscoso      | Spain    | NA    | 66   | itching, discomfort bleeding, dysuria, cramping | right upper vaginal wall | 2                       | WLE + LND | none             | I     | negative| 12            | NED       | +    | -   | +   | +   | -   | -  |    |
| 2022 | Sabri        | USA      | NA    | 62   | bleeding, dysuria, cramping | left labia minor | 3                       | none      | CCRT             | IV    | NA      | NA            | NED       | +    | -   | +   | +   | -   | -  |    |
Table 2 (continued)

| Year   | First Author | Country       | Race | Age | Symptom | Location                  | Maximum tumor size (cm) | Operation | Adjuvant therapy | Stage | LN meta | Follow (month) | Prognosis | CK20 | CK7 | CEA | CDX2 | p16 | ER | PR |
|--------|--------------|---------------|------|-----|---------|----------------------------|------------------------|------------|-------------------|-------|---------|----------------|-----------|------|-----|-----|-----|-----|----|-----|
| 2022   | present case | Japan         | Asian | 63  | vulvar mass | posterior vulva (7 o'clock) | 1                      | WLE        | none              | I     | negative | 27             | NED       | +    | +   | NA  | +   | +   | -  | -   |

UK United Kingdom, USA United States of America, WLE Wide local excision, RV Radical vulvectomy, PE Pelvic exenteration, Chemo Chemotherapy, PTX Paclitaxel, CDDP Cisplatin, CBDCA Carboplatin, CCRT Concurrent chemoradiotherapy, RT Radiation therapy, LN Lymph node, NED No evidence of disease, DOD Died of disease, NA Not available
cases of adenocarcinoma of intestinal-type of the vulva are considered to have a good prognosis, but it may be possible to redefine some of them as “adenoma.”

IHC plays an important role in diagnosis. It is necessary to exclude metastatic gastrointestinal cancers, such as metastatic colorectal cancer. Typically, normal intestinal epithelium is CK7 negative, CK20 positive, and CDX2 positive. Most colorectal cancers are CK7 negative, CK20 positive, and CDX2 positive, while rectal cancers tend to be CK7 positive [35]. The present case was also CK7-positive. In previous reports, among the 21 cases in which IHC for CK20 and CK7 were performed, 20 cases (95%) were positive for CK20 and 13 cases (62%) were positive for CK7 (Table 2). CDX2 is expressed in the mucosal epithelium from the duodenum to the rectum and is also positive in intestinal-type neoplasms of the lower female genital tract. In previous reports, IHC for CDX2 was positive in all eight cases in which it was performed (Table 2). ER and PgR were mostly negative, as observed in the present case (Table 2). Notably, p16 was positive in the present case. Five other cases had IHC findings for p16, four cases of which were positive (Table 2). In another report, reverse transcription polymerase chain reaction for HPV in p16-positive adenocarcinoma of intestinal-type of the vulva did not detect HPV type 16, but only low-risk HPV [29]. HPV was negative in the present case. The significance of HPV status is unclear and further study is needed. In the present case, p53 staining was null, which may reflect the TP53 mutation described below.

The surgical technique for intestinal-type neoplasms of the vulva has not been established; however, complete resection with sufficient margin is presumed to be important. Although there is one report of a patient who received neoadjuvant chemotherapy followed by surgery [21], most cases are preceded by surgery (Table 2). The most common surgical techniques are wide local excision and radical vulvectomy, with lymph node dissection in some cases (Table 2). In the present case, the lesion was less than 2 cm grossly and there were no suspicious findings of lymph node or distant metastasis on imaging. Because the depth of invasion could not be accurately determined by biopsy, wide local excision was performed. There was a sufficient margin, and no adjuvant therapy was performed. For most other cases in which tumors were removed by surgery, adjuvant therapy was not used (Table 2).

Notably, a variety of cancer-associated mutations were detected in the current case. TP53, KEL, RBI, RNF43, and PTEN mutations showed high variant allele frequency and were considered clonal mutations. The variant allele frequencies for PIK3CA and GNAS mutations were very low and were considered to be subclonal mutations. In 2019, Shuangshoti et al. reported tubulovillous adenoma of the vagina with KRAS and APC mutations, despite the absence of high-grade dysplasia or adenocarcinoma [36]. This type of neoplasia may have accumulated cancer-associated genetic mutations in an early stage of evolution. In the gastrointestinal tract, except the colorectum, the histopathologic pattern of adenocarcinoma of intestinal-type is common in the esophagus [35], stomach [37], and duodenal papilla [38]. Outside of the gastrointestinal tract, adenocarcinoma of intestinal-type is most common in the sinuses and is the second most common histologic type of primary sinus cancer [39]. Rare cases of adenocarcinoma of intestinal-type of the tongue [40], gallbladder [41], lung [42], bladder [43], and ureter [44] as primary sites have been reported. In cancers with histopathology showing adenocarcinoma of intestinal-type, TP53 and KRAS mutations are often detected. TP53 mutations are particularly frequent in adenocarcinoma of intestinal-type of the stomach and primary sinus [39, 45]. Among adenocarcinomas of intestinal-type of the duodenal papilla, TP53 and KRAS mutations were reported in approximately 40% of cases and RNF43 mutations in approximately 15% of cases [38]. Another study reported mutations in KRAS, PIK3CA, and SMAD4 [46]. In intraductal papillary mucinous neoplasms of the pancreas of the intestinal type, the frequency of KRAS mutations is approximately 50% [47]. There is also a report of adenocarcinoma of intestinal-type with KRAS mutation arising from a mature cystic teratoma of the ovary [48]. In contrast, KRAS and BRAF mutations are rare in adenocarcinomas of intestinal-type of the sinus [39].

The present case was a precancerous lesion and not treated with adjuvant therapy. However, if the patient was in an advanced stage or had a recurrence with malignant transformation, additional treatment options may have needed to be considered. Potentially actionable genetic mutations found in this case may help establish effective targeted therapy. Loss or activation mutations in PTEN activate the phosphoinositide 3-kinases (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway [49] and predict sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors [50]. PIK3CA mutation also activates the PI3K/AKT/mTOR pathway [49]. Therefore, depending on the course of the disease, the combination of mTOR inhibitors or PARP inhibitors may be considered. GNAS mutations activate ERK/MAPK signals [51]. In this case, a mitogen-activated protein kinase inhibitor may have been useful.

In the present case, TMB was high, at 13 Mut/Mb. TMB is an indicator of response to immunotherapy [52]. The KEYNOTE-158 study showed that advanced solid tumors with TMB ≥10 were more likely to respond to pembrolizumab, an anti-PD-1 antibody [53]. If the patient had been...
in an advanced stage or had a recurrence with malignant transformation, an immune checkpoint inhibitor like pembrolizumab may have been a treatment option. Therefore, in intestinal-type neoplasms of the vulva, a gene panel test may be helpful to select treatment options. In addition, while present case was microsatellite stable, some reports have shown that microsatellite instability–high and mismatch repair deficiency is more frequent in gastric adenocarcinoma of intestinal-type [54, 55], and microsatellite status and IHC for mismatch repair protein may also be checked in intestinal-type neoplasms of the vulva.

In conclusion, here we report a case of tubulovillous adenoma with high-grade dysplasia of the vulva harboring multiple cancer-associated mutations and high TMB. In cases of intestinal-type neoplasms of the vulva, it may be helpful to check TMB and gene mutations for treatment selection.

Abbreviations
IHC: Immunohistochemistry; TMB: Tumor mutational burden; HE: Hematoxylin–eosin; CK: Cytokeratin; ER: Estrogen receptor; PgR: Progesterone receptor; HPV: Human papillomavirus; PI3K: Phosphoinositide 3-kinases; AKT: Protein kinase B; mTOR: Mammalian target of rapamycin; PARP: Poly (ADP-ribose) polymerase; Mut/Mb: Mutations/megabase; MSI: Microsatellite instability.

Authors’ contributions
HS and KM managed the patient and wrote the original draft. TO participated in the pathological evaluation. NM reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding
The authors declare that they have no financial support.

Availability of data and materials
All data generated or used during the study are available from the corresponding author by request.

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Obstetrics and Gynecology, Kindai University Faculty of Medicine, 377-2 Ohnohigashi, Osakasayama, Osaka, Japan. 2 Department of Pathology, Yachiyo Hospital, Anjo, Aichi, Japan.

Received: 17 September 2022 Accepted: 14 October 2022
Published online: 28 October 2022

References
1. Wohlmuth C, Wohlmuth-Wieser I. Vulvar malignancies: an interdisciplinary perspective. J Dtsch Dermatol Ges. 2019;17:1257–76.
2. Lulęnski CR, Naji AF. Mucin-secreting adenocarcinoma of Bartholin gland. report of a case. Obstet Gynecol. 1964;24:542–4.
3. Tiltman AJ, Knutzen VK. Primary adenocarcinoma of the vulva originating in misplaced cloacal tissue. Obstet Gynecol. 1978;51:306–333.
4. Kennedy JC, Majumdar B. Primary adenocarcinoma of the vulva, possibly cloacogenic. A report of two cases. J Reprod Med. 1993;38:113–6.
5. Kaltenbecker B, Manos R, McCall M, Spazarak P. Intestinal-type adenocarcinoma of the vulva: a case study. Gynecol Oncol Rep. 2019;28:133–5.
6. Fox H, Wells M, Harris M, McWilliam LJ, Anderson GS. Enteric tumours of the lower female genital tract: a report of three cases. Histopathology. 1988;12:167–76.
7. Mortensen BB, Nielsen K. Tubulo-villous adenoma of the female genital tract: a case report and review of literature. Acta Obstet Gynecol Scand. 1991;70:161–3.
8. Ghamande SA, Kasznica J, Griffiths CT, Finkler NJ, Hamid AM. Mucinous adenocarcinomas of the vulva. Gynecol Oncol. 1995;57:117–20.
9. Nagar HA, McKinney KA, Price JH, McClelland HR, Biggart JD. Enteric epithelium progressing through dysplasia to adenocarcinoma within the vagina. Eur J Surg Oncol. 1999;25:106–7.
10. Willén R, Békássy, Carlén B, Bozoky B, Cajander S. Cloacogenic adenocarcinoma of the vulva. Gynecol Oncol. 1999;74:298–301.
11. Mudhar HS, Smith JH, Tidy J. Primary vaginal adenocarcinoma of intestinal type arising from an adenoma: case report and review of the literature. Int J Gynecol Pathol. 2001;20:204–9.
12. Zaidi SN, Conner MG. Primary vulvar adenocarcinoma of cloacogenic origin. South Med J. 2001;94:744–6.
13. Rodriguez A, Isaac MA, Hidalgo E, Márquez B, Nogales FF. Villo glandular adenocarcinoma of the vulva. Gynecol Oncol. 2001;83:409–11.
14. Liu SH, Ho CM, Huang SH, Shih BY, Lee FK. Cloacogenic adenocarcinoma of the vulva presenting as recurrent Bartholin’s gland infection. J Formos Med Assoc. 2003;102:49–51.
15. Dubé V, Veilleux C, Plante M, Télu B. Primary villo glandular adenocarcinoma of cloacogenic origin of the vulva. Hum Pathol. 2004;35:377–9.
16. Lee SE, Park NH, Park IA, Kang SB, Lee HP. Tubulo-villous adenoma of the vagina. Gynecol Oncol. 2005;96:556–8.
17. Tjalma WA, Colpaert CG. Primary vaginal adenocarcinoma of intestinal type arising from a tubulovillous adenoma. Int J Gynecol Cancer. 2006;16:1461–5.
18. Cormio G, Carriero C, Loizzi V, Gissi F, Leone L, Putignano G, et al. “Intestinal-type” mucinous adenocarcinoma of the vulva: a report of two cases. Eur J Gynaecol Oncol. 2012;33:433–5.
19. Karkouche R, Ansart F, Tetis B, Lavenu MC, Plantier F. Multiple tubulovillous adenomas of the vulva. Int J Gynecol Pathol. 2012;31:321–4.
20. van Wessel S, Van Kerrebroeck H, Van Bogaert V, Tummers P, Van den Broecke R. Primary intestinal type adenocarcinoma of the female genital tract, arisen from a tubulo-villous adenoma: case report. Gynecol Oncol Case Rep. 2013;3:63–5.
21. Musella A, Marchetti C, Salerno L, Vertechy L, Iadarola R, Pecorella I, et al. Primary villoglandular mucinous adenocarcinoma after neoadjuvant chemotherapy: a case report and a literature review. Case Rep Obstet Gynecol. 2013;4:27141.
22. Suı Y, Zou J,Batchu N, Lv S, Sun C,Du J, et al. Primary mucinous adenocarcinoma of the vulva: a case report and review of the literature. Mol Clin Oncol. 2016;4:545–8.
23. Tepeoğlu M, Uner H, Haberal AN, Özlen Ö, Kuşçu E. Cloacogenic adenocarcinoma of the vulva: a case report and review of the literature. Turk J Pathol Derg. 2018;34:255–8.
24. Matsuzaki A, Saio M, Kosuge N, Aoyama H, Tamaki T, Matsumoto H, et al. Enteric tumours of the lower female genital tract: a report of three cases. Histopathology. 2006;16:1461–5.
25. Musella A, Marchetti C, Salerno L, Vertechy L, Iadarola R, Pecorella I, et al. Primary villoglandular mucinous adenocarcinoma of the vulva. Case Rep Pathol. 2017;2017:1765460.
26. Lee IH, Kim MK, Lee YK, Hong SR, Lee KH. Primary mucinous adenocarcinoma of the vulva, intestinal type. Obstet Gynecol Sci. 2017;60:369–73.
27. He SR, Deng WH, Yang L, Yang K, Cui D, Liu DG. Cloacogenic adenocarcinoma of the vulva: one new case and literature review. Eur J Gynaecol Oncol. 2017;38:296–302.
28. Kunita T, Matsuura Y, Hisaoka M, Hachisuaga T. Adenocarcinoma of intestinal type of the vulva. Int J Cancer Con J. 2019;8:89–93.
29. Uygur AO, Haruna M, Okunade KS, Ohaaziker E, Anorlu RI, Banjo AAF. Primary vaginal adenocarcinoma of intestinal-type: case report of a rare gynaecological tumour. Oxf Med Case Rep. 2019;2019:omz088.
Moscocos O, Reques A, Saco A, Castellvi J, Gómez-Hidalgo NR, Ramón Y Cajal S, et al. Vulvar adenocarcinoma of intestinal type: a case report of an uncommon entity. Int J Gynecol Pathol. 2020;29:491–503.

30. Sabín A, Li C, Monika F, Sharma A, Sharma P. Primary vaginal adenocarci-

noma of intestinal-type: a case report of a rare tumor with review of histo-

logy, differential diagnosis, and literature. Cureus. 2022;14:e25298.

31. Staats PN, McCluggage WG, Clement PB, Young RH. Primary intestinal-

type glandular lesions of the vagina: clinical, pathologic, and immunohis-

tochemical features of 14 cases ranging from benign polyp to adenoma
to adenocarcinoma. Am J Surg Pathol. 2014;38:593–603.

32. Wilkinson EJ, Rush DS. Precursor lesions and malignant tumors of the

vulva: blustein’s pathology of the female genital tract. 7th ed. New York: Springer; 2019.

33. WHO Classification of Tumours Editorial Board. Digestive system tumours. 5th ed. Lyon: International Agency for Research on Cancer. 2019.

34. Vitrey D, Frachon S, Balme B, Gollier F. Tubulovillous adenoma of the vulva. Obstet Gynecol. 2003;102:160–3.

35. Urabe M, Ushiku T, Shinozaki-Ushiku A, Iwasaki A, Yamazawa S, Yamashita Y, et al. Adenocarcinoma of the esophago gastric junction and its background mucosal pathology: a comparative analysis according to Siewert classification in a Japanese cohort. Cancer Med. 2018;7:5145–54.

36. Shaungshong T, Tearapakpinyo C. Tubulovillous adenoma of vagina with both KRAS and APC Mutations: case report. Int J Gynecol Pathol. 2019;38:498–501.

37. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.

38. Lundgren S, Hau SO, Bebro J, Heby M, Karnevi E, Nordin B, et al. Muta-
tional landscape in resected perianual adenocarcinoma: relationship with morphology and clinical outcome. JCO Precis Oncol. 2019;3. https://doi.org/10.1200/PO.18.00323.

39. Leivo I. Intestinal-type adenocarcinoma: classification, immunopheno-
type, molecular features and differential diagnosis. Head Neck Pathol. 2017;11:295–300.

40. Rahimi S, Akaev I, Repanos C, Brennan PA, Dubois JD. Primary intestinal-
type adenocarcinoma of tongue: a case report with immunohistochemi-
cal and molecular profiles and review of the literature. Head Neck Pathol. 2017;11:186–91.

41. You J, Bui K, Bui MM, Malafa M, Coppola D. Histopathological and immunophenotypical features of intestinal-type adenocarcinoma of the gallbladder and its precursors. Cancer Control. 2014;21:247–50.

42. Sotojc D, Koncic M, Subotic D, Popovic M, Tomasevic D, Lukic J. Intestinal type of lung adenocarcinoma in younger adults. Case Rep Pulmonol. 2014;2014:282196.

43. Santos BM, de Souza JD, Lima RS, de Lima EM. Mucinous bladder adenocarcinoma: case report and literature review. Case Rep Urol. 2015;2015:783109.

44. Kato H, Hayama M, Kobayashi M, Ota H, Nishizawa O. Large intestinal
type-urachal adenocarcinoma with focal expression of prostatic specific antigen. Int J Urol. 2004;11:1033–5.

45. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.

46. Shuangshoti S, Teerapakpinyo C. Tubulovillous adenoma of the vagina: case report and literature review. Case Rep Urol. 2014;2014:282196.

47. Lundgren S, Hau SO, Bebro J, Heby M, Karnevi E, Nordin B, et al. Muta-
tional landscape in resected perianual adenocarcinoma: relationship with morphology and clinical outcome. JCO Precis Oncol. 2019;3. https://doi.org/10.1200/PO.18.00323.

48. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.

49. Lundgren S, Hau SO, Bebro J, Heby M, Karnevi E, Nordin B, et al. Muta-
tional landscape in resected perianual adenocarcinoma: relationship with morphology and clinical outcome. JCO Precis Oncol. 2019;3. https://doi.org/10.1200/PO.18.00323.

50. You J, Bui K, Bui MM, Malafa M, Coppola D. Histopathological and immunophenotypical features of intestinal-type adenocarcinoma of the gallbladder and its precursors. Cancer Control. 2014;21:247–50.

51. Sotojc D, Koncic M, Subotic D, Popovic M, Tomasevic D, Lukic J. Intestinal type of lung adenocarcinoma in younger adults. Case Rep Pulmonol. 2014;2014:282196.

52. Santos BM, de Souza JD, Lima RS, de Lima EM. Mucinous bladder adenocarcinoma: case report and literature review. Case Rep Urol. 2015;2015:783109.

53. Kato H, Hayama M, Kobayashi M, Ota H, Nishizawa O. Large intestinal
type-urachal adenocarcinoma with focal expression of prostatic specific antigen. Int J Urol. 2004;11:1033–5.

54. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.

55. Rahimi S, Akaev I, Repanos C, Brennan PA, Dubois JD. Primary intestinal-
type adenocarcinoma of tongue: a case report with immunohistochemi-
cal and molecular profiles and review of the literature. Head Neck Pathol. 2017;11:186–91.

56. You J, Bui K, Bui MM, Malafa M, Coppola D. Histopathological and immunophenotypical features of intestinal-type adenocarcinoma of the gallbladder and its precursors. Cancer Control. 2014;21:247–50.

57. Sotojc D, Koncic M, Subotic D, Popovic M, Tomasevic D, Lukic J. Intestinal type of lung adenocarcinoma in younger adults. Case Rep Pulmonol. 2014;2014:282196.

58. Santos BM, de Souza JD, Lima RS, de Lima EM. Mucinous bladder adenocarcinoma: case report and literature review. Case Rep Urol. 2015;2015:783109.

59. Kato H, Hayama M, Kobayashi M, Ota H, Nishizawa O. Large intestinal
type-urachal adenocarcinoma with focal expression of prostatic specific antigen. Int J Urol. 2004;11:1033–5.

60. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.

61. Rahimi S, Akaev I, Repanos C, Brennan PA, Dubois JD. Primary intestinal-
type adenocarcinoma of tongue: a case report with immunohistochemi-
cal and molecular profiles and review of the literature. Head Neck Pathol. 2017;11:186–91.

62. You J, Bui K, Bui MM, Malafa M, Coppola D. Histopathological and immunophenotypical features of intestinal-type adenocarcinoma of the gallbladder and its precursors. Cancer Control. 2014;21:247–50.

63. Sotojc D, Koncic M, Subotic D, Popovic M, Tomasevic D, Lukic J. Intestinal type of lung adenocarcinoma in younger adults. Case Rep Pulmonol. 2014;2014:282196.

64. Santos BM, de Souza JD, Lima RS, de Lima EM. Mucinous bladder adenocarcinoma: case report and literature review. Case Rep Urol. 2015;2015:783109.

65. Kato H, Hayama M, Kobayashi M, Ota H, Nishizawa O. Large intestinal
type-urachal adenocarcinoma with focal expression of prostatic specific antigen. Int J Urol. 2004;11:1033–5.

66. Network CGAR. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.

67. Rahimi S, Akaev I, Repanos C, Brennan PA, Dubois JD. Primary intestinal-
type adenocarcinoma of tongue: a case report with immunohistochemi-
cal and molecular profiles and review of the literature. Head Neck Pathol. 2017;11:186–91.

68. You J, Bui K, Bui MM, Malafa M, Coppola D. Histopathological and immunophenotypical features of intestinal-type adenocarcinoma of the gallbladder and its precursors. Cancer Control. 2014;21:247–50.