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Original Article

Primary renal mucinous cystadenocarcinoma coexistent with a carcinoid element, probably arising from the renal pelvis

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Abstract: Here, we report a case of primary renal mucinous cystadenocarcinoma coexistent with a carcinoid element in a 33-year-old woman who presented with a complaint of intermittent pain in the left flank. Grossly, the tumor was a unilocular cystic mass filled with abundant yellowish mucinous or gelatinous material. Microscopically, the cyst wall was mostly lined with atypical mucinous epithelium showing varying degrees of stratification, tufting, and slender papillae and focally, a cribriform pattern was observed. Intestinal metaplasia was present, in addition to a smooth transition from the normal urothelium to the atypical mucinous epithelium. Small nests of neuroendocrine-like cells were scattered in foci in the cyst wall. The immunophenotype (CK20-, MUC2-, CDX2-, and Villin-positive) of the mucinous epithelium confirmed its intestinal phenotype. The majority of cells in the carcinoid portion of the tumor stained positive for AE1/AE3, Synaptophysin, CD56, and Chromogranin. This tumor probably arose from the renal pelvis. The patient underwent left radical nephrectomy. At the last follow-up, this patient was doing well, with no evidence of recurrence.

Keywords: Kidney neoplasm, mucinous cystadenocarcinoma, carcinoid tumor, renal pelvis

Introduction

Primary mucinous epithelial tumors and neuroendocrine tumors (NETs) of the kidney have been rarely reported in the literature. To date, few cases of mucinous cystic neoplasms of the kidney [1-7] and renal carcinoid tumors [8-12] have been reported. Only 2 previous cases of a primary renal carcinoid tumor with a mucinous cystadenoma element have been described [13, 14]. However, no case of a composite kidney tumor composed of a malignant mucinous epithelial element and carcinoid element has been reported. To our knowledge, this is the first report of a primary renal mucinous cystadenocarcinoma coexistent with a carcinoid element that likely arose from the renal pelvis.

Materials and methods

Case presentation

A 33-year-old Asian woman with no previous history of renal neoplasm presented with a 6 month history of intermittent pain in the left flank without dysuria, urination, hematuria or fever. General physical examination revealed no positive findings. Abdominal computed tomography revealed a cystic and hypodense mass involving the middle and lower portion of the left kidney, with extension to the renal hilum, measuring 8.3×7.8×6.6 cm. The mass was characterized by scattered nodular and eggshell-like calcifications at its edges (**Figure 1A**). Imaging did not reveal any other mass or ascites in the abdomen. There was no evidence of extrarenal spread or distant metastasis. The primary clinical diagnosis was a renal parenchymal cyst. Left radical nephrectomy was performed. No residual, recurrent, or metastatic tumor was identified at the most recent follow-up at 24 months after surgery. There was no evidence of lesions in the pancreas, appendix or ovaries.

Immunohistochemistry

Immunohistochemical analysis was performed using the standard EnVision technique with a

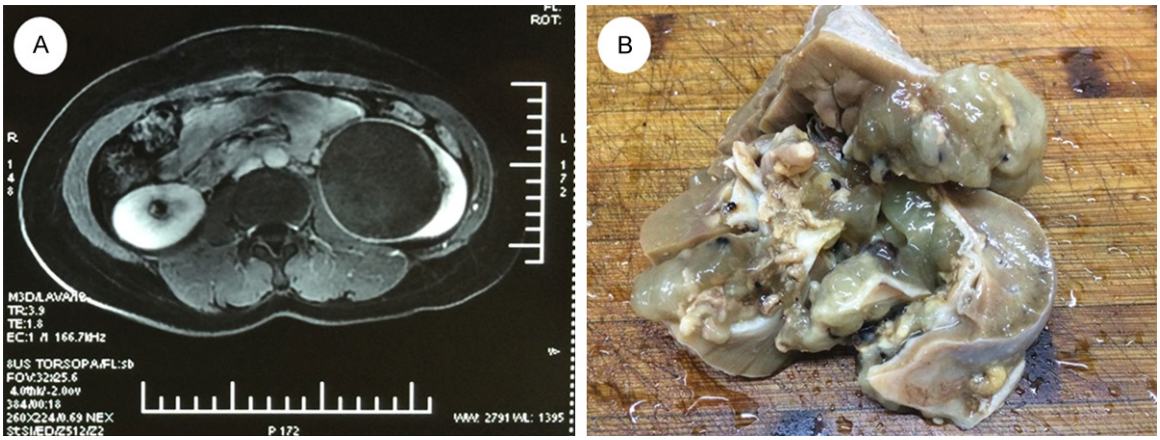

Figure 1. A. Computed tomography (CT), showing a large cyst arising from the left kidney. B. The cyst was filled with abundant yellowish mucinous or gelatinous material.

panel of antibodies, including cytokeratin (AE1/AE3) (1:100; Dako), cytokeratin 7 (CK7) (1:50; Dako), CK20 (1:100; Dako), CDX2 (1:100; Dako), MUC2 (1:100; Dako), CEA (1:50; Dako), Villin (1:100; Dako), CA125 (1:100; Dako), ER (1:100; Dako), PR (1:100; Dako), GATA binding protein 3 (GATA-3) (1:100; Santa Cruz), Paired box gene 2 (PAX2) (1:3000; Abcam), Paired box gene 8 (PAX8) (1:800; Proteintech Group), Synaptophysin (1:100; Dako), Chromogranin A (1:100; Dako), CD56 (1:100; Dako), Ki-67 (1:100; Dako), and Thyroid Transcription Factor-1 (TTF-1) (1:100; Dako). Appropriate positive and negative controls for each antibody were used throughout the study.

Results

Pathological findings

Grossly, the tumor was a well-defined unilocular cystic mass that measured 8.0×7.5×6.6 cm in size and was located in the lower half of the kidney. It was filled with abundant yellowish mucinous or gelatinous material, and a small calcification was present in the lumen (**Figure 1B**). The cut surface of the tumor was soft, fragile, elastic and greyish-white in color. The inner surface of the cyst was grayish-white and rather smooth and glistening with no papillary projections. The cyst wall was 0.1-0.2 cm thick and was directly attached to the parenchyma of the renal medulla. The residual renal pelvis and ureter were well preserved.

Microscopically, the fibrous cyst wall contained large pools of mucin, focal eosinophilic amorphous material with degeneration and necrosis, aggregates of foamy and hemosiderin-laden histiocytes, multinucleated giant cells, cholesterol clefts and focal calcification. The adjacent renal parenchyma was atrophic in appearance and characterized by glomerular sclerosis, interstitial fibrosis, and mild inflammation.

Most areas of the cyst were lined with stratified columnar epithelium containing goblet cells with stratified, enlarged, irregular and hyperchromatic nuclei and vacuolated cytoplasm. Mitotic figures were easily identifiable, and abnormal mitotic figures were present. The epithelium exhibited varying degrees of stratification, tufting, and slender papillae and focally, a cribriform pattern was observed (**Figure 2A-D**). Furthermore, foci of signet ring cells were observed lying in mucin pools (**Figure 2E**). In some sections, tumor cells had invaded the fibrous stroma and were arranged as irregular glands, cords, or single cells with malignant cytological features (**Figure 2F**). Abundant extracellular mucin had infiltrated into the fibrous stroma and focally formed mucin pools. The surrounding stroma showed desmoplasia and contained small atrophic renal tubules and glomeruli. No necrosis, vascular invasion, or perirenal fat invasion was observed.

Areas of benign and borderline histology coexisted in the same sections. Parts of the epithelium had a single-layered low columnar histology without obvious atypia, with gradual transition to an area of tall columnar mucinous epithelium resembling intestinal and endocer-

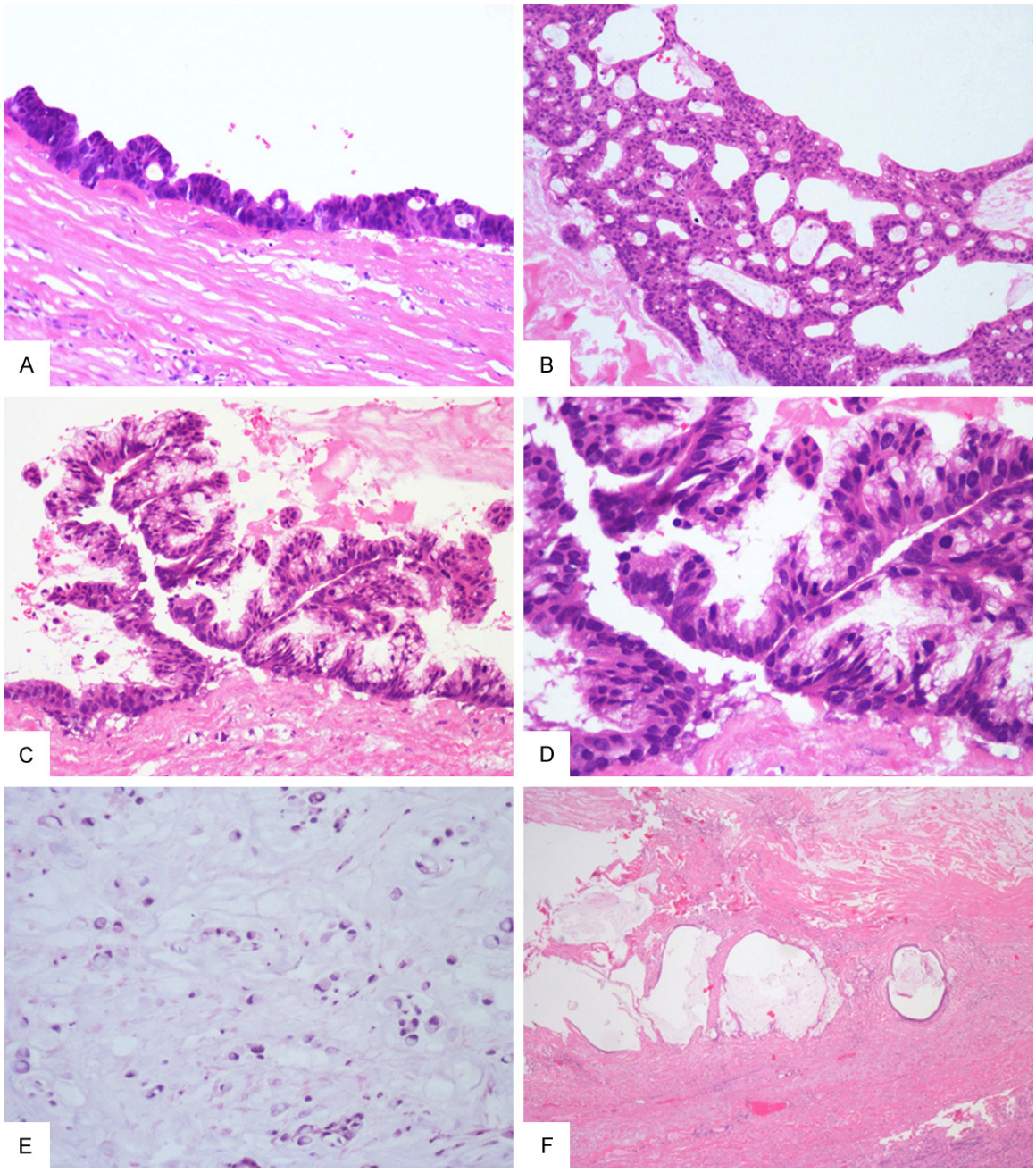

Figure 2. Complex architecture: stratification (A), cribriform pattern (B) and slender papillae (C). Higher-power magnification, showing nuclear atypia and mitotic figures (D). Signet ring cells lying in mucin pools (E). Tumor cells had invaded the fibrous stroma and were arranged as irregular glands (F).

vical epithelium. Papillary foci were also noted. Other areas of the epithelium had varying degrees of stratification, tufting and slender papillae, with mildly to moderately atypical cells and scattered goblet cells that were enlarged and hyperchromatic. Few mitotic cells were present. In one focal area, intestinal metaplasia and a transition zone from the normal urothelium to atypical mucinous epithelium were observed (**Figure 3A**). The urothelial lining of the rest of the cyst and the renal pelvis was not involved by flat or papillary urothelial carcinoma.

Further, small nests of neuroendocrine-like cells were focally scattered in the fibrous mesenchyma of the cyst wall, with a maximum diameter of 3 mm. Tumor cells were uniform

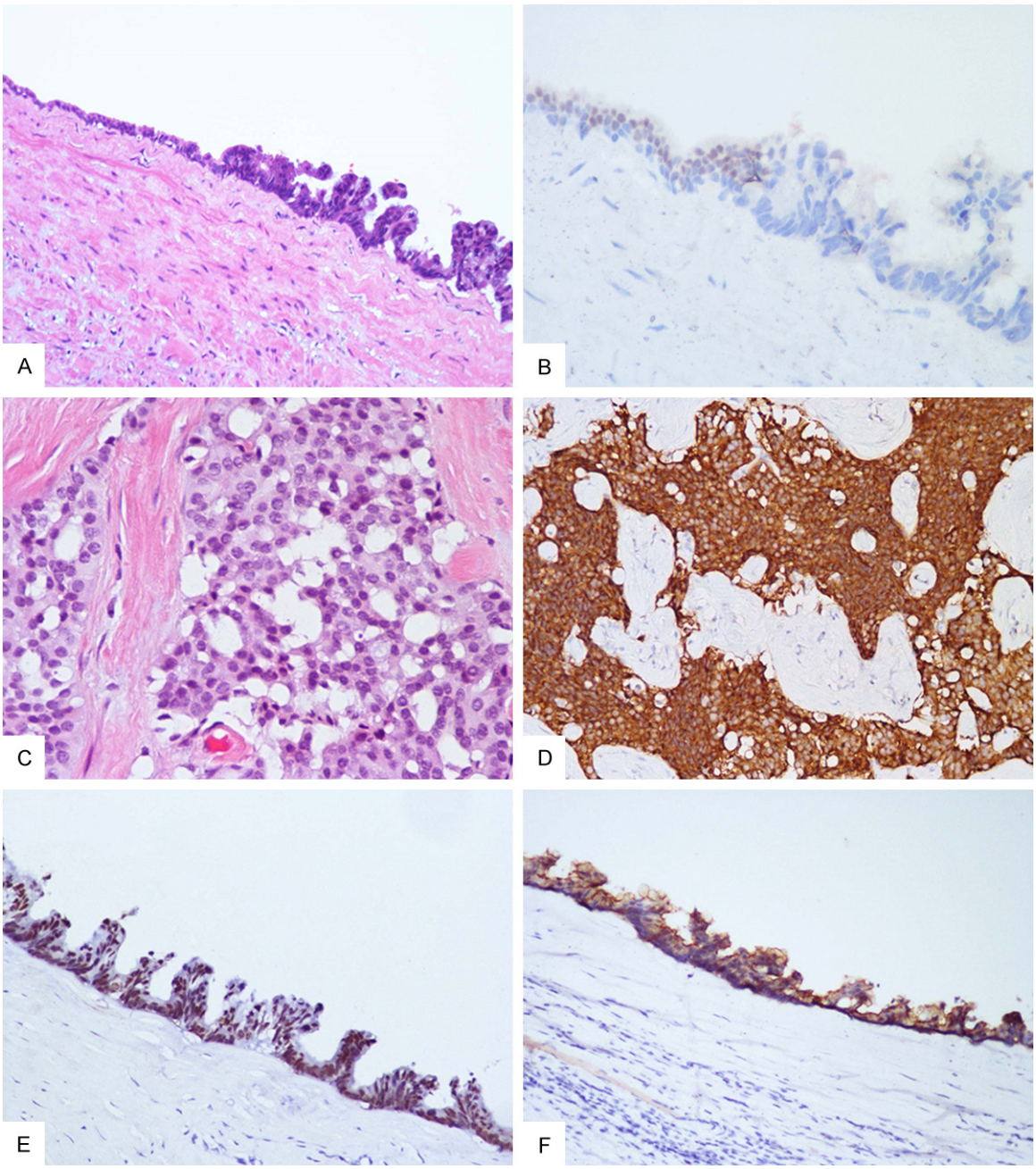

Figure 3. (A) The transition between the normal urothelium (left) and neoplastic epithelium (right). (B) The normal urothelium stained positive for GATA-3, but the neoplastic epithelium was negative for this protein. Microscopic features of the carcinoid tumor (C) and Synaptophysin immunostaining (D). Diffuse and strong nuclear immunoreactivity for CDX2 (E) and cytoplasmic immunoreactivity for Villin (F).

and small in size and were round to polygonal in shape, exhibiting solid and trabecular patterns (**Figure 3C**).

Immunohistochemical findings

Mucinous epithelial cells demonstrated strong and diffuse immunoreactivity with antibodies against CDX2 (**Figure 3E**), MUC2, CK20, CEA, and Villin (**Figure 3F**), slight focal positivity for CK7, and uniform negativity for CA125, PAX2, PAX8, ER, and PR. Proliferative activity, as assessed using Ki-67, was approximately 80%. The residual normal urothelium was positive for GATA-3, but the neoplastic epithelium tested negative for this protein (**Figure 3B**).

Table 1. Summary of patients with composite tumor of mucinous cystic neoplasm and carcinoid of the kidney

Reference	Age (y)	Sex	Tumor site	Medical history	Carcinoid symptoms	Mucinous cystic tumor size (cm)[a]	Carcinoid tumor size (cm)[a]	Pathology diagnosis	Surgery	Follow-up (mo)	Outcome
Takashi et al [4]	53	Female	Right kidney	Pyelolithotomy for right renal lithiasis	No	2.7	1.5	Composite tumor of mucinous cystadenoma and somatostatinoma of the kidney	RN	21	ANED
Kawahara et al [5]	50	Male	Right kidney	No	No	4.5	2.2	Primary renal carcinoid tumor with a mucinous cystadenoma element	RN	NA	NA
Our case	33	Female	Left kidney	No	No	8.0	0.3	Primary renal mucinous cystadenocarcinoma coexistent with a carcinoid tumor element	RN	24	ANED

Abbreviations: RN, radical nephrectomy; NA, not available; ANED, alive with no evidence of disease. [a]Largest dimension.

The neuroendocrine-like element was diffusely and strongly positive for AE1/AE3, Synaptophysin (**Figure 3D**), and CD56 and focally positive for Chromogranin. Ki-67 staining indicated low proliferative activity of below 1%. Tumor cells of the neuroendocrine-like element were negative for TTF-1 and the above-mentioned intestinal markers, and they exhibited no immunoreactivity for CA125, PAX2, PAX8, ER, PR, or GATA-3.

Discussion

Mucinous cystic neoplasms of the kidney are exceedingly rare. Due to the rarity of this tumor type and the limited number of reported cases [1-7], it has not been formally recognized in the WHO classification of tumors of the urinary system. Primary carcinoid tumors of the kidney are also uncommon [8-12]. Only 2 cases of renal composite tumors composed of mucinous cystadenoma and carcinoid elements have been reported previously. Takashi et al [13] reported a case of a composite tumor of mucinous cystadenoma and carcinoid elements in the right kidney. Kawahara et al [14] described a primary renal carcinoid tumor with a mucinous cystadenoma element in the right kidney. Both of those tumors were lined with benign epithelium. In contrast, in the current case, the tumor was mainly composed of malignant mucinous epithelium. Therefore, our case is the first documented composite tumor composed of mucinous cystadenocarcinoma and carcinoid elements arising in the kidney. The clinical features of these 3 cases are summarized in **Table 1**. All patients had no carcinoid symptoms and one patient had a history of nephrolithiasis. The ages of these patients at diagnosis were 53 years, 50 years and 33 years, respectively, and the maximum diameters of the whole tumors were 2.7 cm, 4.5 cm and 8.0 cm. All patients underwent radical nephrectomy. Follow-up data were available for 2 patients, who are now well without recurrence at 21 months and 24 months after their operations. No lesions were evident in the pancreas, appendices or ovaries and there was no evidence of extrarenal spread or distant metastasis in both of the two patients.

For the diagnosis of renal mucinous tumors, we referred to the microscopic criteria for evaluating mucinous ovarian tumors [15]. The pathological diagnosis of mucinous cystadenocarcinoma was made based on the microscopic features of malignant intestinal-type epithelial cells containing intra-cytoplasmic mucin, mitotic figures and stromal invasion. The histological features of primary renal carcinoid tumors are similar to the NETs of those anatomical locations. Therefore, the new 2016 WHO classification propose classifying primary renal carcinoid tumors in a manner similar to the classification of carcinoid tumors at other anatomical locations and recommend renal carcinoid and atypical carcinoid tumors should be newly designated as well-differentiated neuroendocrine tumors of the kidney [16]. The number of mitotic cells, the proliferation index (Ki-67) and other immunohistochemical markers play important roles in the diagnosis of renal carcinoid tumors. In the current case, the neuroendocrine-like areas had a mitotic activity of <2/10 high-power fields, a Ki-67 index of <2%, and positive reactivity to AE1/AE3, Synaptophysin, CD56 and Chromogranin, and they lacked renal-specific transcription factors, such as PAX-2 and PAX-8 [12]; therefore, the tumor was classified as well-differentiated tumors.

Because of the rarity of the renal carcinoid tumor type and the similarity of its histology with those of carcinoid tumors of other origins, it is essential to rule out the possibility of a metastatic tumor originating from another location, such as the pancreas, ovary, uterine cervix, gastrointestinal tract or appendix, before classifying a renal carcinoid tumor as a primary tumor. Notably, in our case, the tumor was found to have originated from the kidney. First, extensive post-operation work-up, including gastrointestinal endoscopy, chest and abdominal CT scans and pelvic and female reproductive tract ultrasounds, were performed, which did not reveal any additional mass lesions in the above-mentioned organs. Second, intestinal metaplasia was detected, with normal urothelium transitioning to neoplastic epithelium, suggesting that this tumor probably arose from the renal pelvis. Immunohistochemistry confirmed that the neoplastic epithelium expressed intestinal-type markers, but not GATA-3, which is a relatively specific urothelial marker. In addition, areas of benign, borderline and malignant epithelia coexisted, indicating the transition of the tissue from adenoma to adenocarcinoma. These findings suggest that the adenoma-carcinoma sequence may exist among glandular

neoplasms that originate in the renal pelvis. All of these findings support the diagnosis of a primary tumor arising from the kidney rather than a metastasis from another site.

To date, the histogenesis of renal mucinous cystadenocarcinoma coexistent with a carcinoid tumor has not been clarified. Mucinous adenocarcinoma is presumed to originate from intestinal metaplasia of the transitional epithelium, which undergoes malignant transformation. Several mechanisms have been proposed for this transformation, including long-standing chronic inflammation, hydronephrosis and renal calculi, differentiation of the coelomic epithelium, and maldevelopment of the kidney [17]. In the current case, we observed a histological transition from urothelium to metaplastic mucinous areas, with the presence of both of these tissue types within the same lesion. We confirmed that mucinous cystadenocarcinoma, like its benign counterpart, arises from foci of intestinal metaplasia. The following four hypotheses have been proposed to explain the pathogenesis of pure renal carcinoid tumors: (1) they are derived from a primitive/stem cell that undergoes neuroendocrine differentiation via neoplastic activation of gene sequences common to neuroendocrine-programmed cells [18]; (2) they are derived from misplaced or entrapped neural crest tissue (APUD cells) in the hilar (central) aspect of the kidney during embryogenesis [19]; (3) they are derived from interspersed neuroendocrine cells associated with intestinal metaplasia of the pyelocalyceal urothelium (e.g., induced by chronic infection) [19, 20] and (4) they develop within a teratoma or renal anomaly [17, 20-22]. In the present case, we could not find any morphological evidence in support of the last hypothesis, such as squamous epithelium, hair shafts, pancreatic acini, or horseshoe kidney. A previous study has identified neuroendocrine cells in the normal mucosa of the renal pelvis and ureter [23]. Therefore, we presumed that the primary renal mucinous cystadenocarcinoma coexistent with the carcinoid element in this case probably arose from urothelial epithelium with intestinal metaplasia and from pre-existing hyperplasia of neuroendocrine cells located within foci of the metaplastic epithelium or from intramucosal neuroendocrine cells in the renal pelvis.

The prognosis and clinical behavior of these tumors remain unclear. Due to the small volumes and better prognosis of carcinoid tumors without carcinoid symptoms [24], the prognosis of our patient is likely dependent on the mucinous cystadenocarcinoma component of the tumor. The prediction of the prognosis of patients with this tumor type is very difficult, and more cases with longer follow-up durations need to be examined.

In summary, we have described the first case of mucinous cystadenocarcinoma coexistent with a carcinoid element arising primarily in the kidney. Although it is very rare, it represents a unique and distinctive tumor entity that may be classified by the World Health Organization classification system in the future. Therefore, histological and clinical analyses are essential for establishing the diagnosis of this tumor type.

Disclosure of conflict of interest

None.

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