Combination of Nivolumab Plus Ipilimumab for Mucinous Tubular and Spindle Cell Carcinoma of the Kidney with Bone Metastases: The First Case Report

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Case Report

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Abstract

Background: Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare subtype of renal cell carcinoma (RCC) and generally considered a low-grade renal epithelial neoplasm composed of tubules, spindle cells, and extracellular mucin. MTSCC with distant metastases has been reported, with some cases showing a poor prognosis. While only a few case reports regarding the treatment of metastatic MTSCC have been reported, targeted agents and monotherapy of immune checkpoint inhibitors have shown some efficacy. To our knowledge, this is the first reported case of metastatic MTSCC of the kidney treated with combination therapy of nivolumab plus ipilimumab.

Case presentation: A 26-year-old man consulted our hospital after a 72-mm tumor was detected at the upper pole of the left kidney with multiple osteolytic bone metastases by computed tomography (CT). A CT-guided biopsy of the renal tumor and bone metastases resulted in a diagnosis of MTSCC of the kidney with bone metastases (cT2aN0M1) and an ‘intermediate risk’ according to the International Metastatic Renal Cell Carcinoma Database Consortium criteria. He therefore received combination therapy of nivolumab plus ipilimumab therapy. After 4 cycles of combination nivolumab plus ipilimumab and 9 cycles of nivolumab monotherapy, he underwent cytoreductive nephrectomy because the tumor had shrunk, and sclerotic changes in the bone metastases were noted. In the excised specimen, the programmed cell death ligand 1 expression was higher in the spindle components than in the tubular components, but CD4- and CD8-positve T cells showed greater infiltration in the tubular components than in the spindle components. Furthermore, CD-4- and CD-8-positive T cells in both components of the resected specimen showed greater infiltration than they had at the pretreatment biopsy of the renal tumor and bone metastases.

Conclusions: Combination immunotherapy of nivolumab and ipilimumab may be an effective treatment option for metastatic MTSCC of the kidney.

Background

Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare subtype of renal cell carcinoma (RCC) first defined in the 2004 edition of the World Health Organization Classification (1) and generally considered a low-grade renal epithelial neoplasm composed of tubules, spindle cells, and extracellular mucin. Fewer than 100 total cases have been reported in the literature (2). However, with the increasing recognition of MTSCC of the kidney, more cases of MTSCC with distant metastases are being reported, some of which have a poor prognosis. Only case reports have been reported regarding the treatment of metastatic MTSCC, and targeted agents and monotherapy with immune checkpoint inhibitors have shown some efficacy (3–6).

To our knowledge, this is the first case of metastatic MTSCC of the kidney treated with an immune checkpoint inhibitor via combination therapy of nivolumab plus ipilimumab.

Case Presentation

Clinical history

This patient was a 26-year-old man with a 1-month history of intermittent back pain. He went to a hospital because he had asymptomatic gross hematuria. He consulted our hospital because a left renal tumor had been detected by echography and computed tomography (CT). CT revealed a 72-mm tumor at the upper pole of the left kidney, well-circumscribed, that was slightly enhanced heterogeneously in the corticomedullary phase and excretory phase but showed no strong enhancement in the corticomedullary, as is usually observed in clear cell RCC. In addition, multiple osteolytic changes were confirmed in bone (Fig. 1).

A CT-guided biopsy was performed on the left renal tumor, and osteoplastic changes of the second lumbar spine were noted. The left kidney tumor biopsy specimen showed bland tubular structures with focal clear cells, oncocytic changes, and cytoplasmic vacuolation accompanied by necrosis and spindle cells. The stroma had basophilic to eosinophilic mucin, aggregates of plasmacytes, and hyalinization. An immunohistochemical analysis revealed that tumor cells were diffusely positive for CK7, AMACR, and AE1/AE3. The histology and immunohistochemical profile were consistent with MTSCC of the kidney (Fig. 2). The bone biopsy specimen show massive coagulation necrosis with bland tubular structures with focal oncocytic changes, accompanied by spindle cells. These features were similar to those of left renal malignant tumor (Fig. 3). He was diagnosed with MTSCC of the kidney with bone metastases (cT2aN0M1) and an ‘intermediate risk’ according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (he had two prognostic factors [anemia and <1 year since the diagnosis]).

Combination therapy (once every 3 weeks, intravenously) of nivolumab (240 mg/body) and ipilimumab (1 mg/kg) was administered as the first-line therapy. At the same time, 120 mg of denosumab was subcutaneously injected every 4 weeks, and palliative radiotherapy was also performed for bone metastases to control the bone pain in the first cervical vertebra and second lumbar vertebra. After 4 cycles of the combination of nivolumab plus ipilimumab, CT revealed that the non-enhanced area was increased in the left renal tumor, and sclerotic changes had appeared in the bone metastases. Nivolumab monotherapy (once every 2 weeks, 240 mg/body) was subsequently continued. He developed immune-related adverse events (irAEs) after four courses of nivolumab (diarrhea, Grade 3). CT showed no thickening of the intestinal tract. However, colonoscopy showed a slightly edematous mucosa and poor vascular visibility, and a colon biopsy showed colonic mucosa with mild chronic inflammatory infiltration. The diarrhea improved immediately after prednisolone was started at 1 mg/kg/day to control the AEs. Subsequently, nivolumab was restarted, and CT to evaluate the therapeutic effect after eight courses revealed that the left renal tumor had shrunk slightly, and the non-enhanced area was even further increased, as were the osteosclerosis changes in the bone metastases (Fig. 4). Therefore, the patient underwent cytoreductive nephrectomy (laparoscopic radical nephrectomy) after nine courses.

He resumed nivolumab treatment 2 weeks later after surgery and has been receiving nivolumab (480 mg/body) and denosumab every 4 weeks. At present, the observation period is quite short at 12 months, but no progressive disease or irAEs has been observed.

Pathological findings

Grossly, the tumor at the left kidney was mostly necrotic with hemorrhaging and white-toned solid parts (Fig. 5). Histologically, the sections showed biphasic proliferation of a papillary or tubular pattern with atypical epithelial cells and clear or eosinophilic cytoplasm as well as diffuse proliferation of atypical spindle-shaped cells, accompanied by inflammatory cell infiltration and necrosis. Nucleoli were prominent and easily visualized at low-power magnification, showing an International Society of Urological Pathology grade was 3. Mucin was observed in the interstitium of the tumor on alcian blue staining (Fig. 6). An immunohistochemical analysis revealed that the tumor cells of the tubular/spindle components were positive for AE1/AE3(+/+), EMA(+/+), vimentin(+/+), PAX8(+/+), AMACR(+/+) in the resected specimen after nivolumab plus ipilimumab.

In addition, the biopsy of the pretreatment renal tumor and bone metastasis and the resected specimen after nivolumab plus ipilimumab was evaluated by immunostaining of programmed cell death ligand 1 (PD-L1), cytotoxic T lymphocyte–associated antigen-4 (CTLA-4), CD4, and CD8. The PDL-1 expression was higher in the spindle components than in the tubular components, but CD4- and CD8-positve T cells showed greater infiltration in the tubular components than in the spindle components (Fig. 7, 8). Furthermore, CD-4- and CD-8-positive T cells in both components of the resected specimen showed greater infiltration than they had at the pretreatment biopsy of the renal tumor and bone metastases (Fig. 2, 3). There was no marked difference in the CTLA-4 expression between the spindle and tubular components in the resected specimen (Fig. 7, 8).

Genomic findings

The nonsense variant S562* in the FBXW7 gene was reported. The tumor mutation burden was 2.52 mutations per megabase, and microsatellite instability was absent.

Discussion

MTSCC was originally reported as a rare histological type of RCC with low malignant potential (7, 8). Patients with MTSCC of the kidney treated with surgical resection tend to have generally favorable outcomes. However, fatal cases of MTSCC with distant metastases have been reported (9–14). No therapeutic strategy has yet been established for metastatic MTSCC, and the efficacy of targeted agents and monotherapy of immune checkpoint inhibitors has been reported only in a few case reports (3–6).

Ipilimumab is a humanized monoclonal IgG1 anti-cytotoxic T-lymphocyte antigen-4 antibody that, in combination with nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, was recently approved by the Food and Drug Administration as a first-line treatment of IMDC intermediate-

and poor-risk metastatic clear cell RCC after the Checkmate 214 trial showed a significantly improved progression-free survival and overall survival (OS) with combination therapy (15). However, non-clear cell RCC histologies were excluded from the trial, so the activity of nivolumab plus ipilimumab for non-clear cell RCC remains unknown.

According to the National Comprehensive Cancer Network guidelines, sunitinib is a preferred systemic regimen for non-clear cell histology (16). A meta-analysis of three studies concluded that sunitinib results in favorable outcomes compared with everolimus for first-line therapy (17). However, combination therapy of nivolumab plus ipilimumab was chosen in the present case because there was a possibility that combination immunotherapy might be more effective for bone metastases and show a more durable response than targeted agents like sunitinib.

A retrospective analysis of the combination of nivolumab plus ipilimumab for non-clear cell RCC has already been reported in a small sample, but that study did not include MSTCC of the kidney (18). To our knowledge, the present case was the first to be treated with combination therapy of nivolumab plus ipilimumab for MTSCC of the kidney with bone metastases. In addition, the present patient underwent nephrectomy, and the immunological therapeutic effect in the resected specimen was also evaluated.

Impressively, two different components—tubular and spindle—were confirmed in the same preparation of the excised specimen and showed a differing expression on immunohistochemical staining (Fig. 6–8). Staining showed that the PD-L1 expression was higher than in the spindle components in the tubular components. The expression of the immune checkpoint PD-L1 is reportedly increased at the surface of sarcomatoid RCC cells compared to non-sarcomatoid RCC cells, regardless of the parent histology or non-sarcomatoid RCC tumor grade (19, 20).

Regarding sarcomatoid RCC, while a consensus conference discussed the definition of sarcomatoid RCC, no consensus was ultimately obtained (21). The largest percentage (41%) of participants felt that a tumor was sarcomatoid if it consisted of atypical spindle cells and resembled any form of sarcoma. However, another group (22%) considered a tumor sarcomatoid if it had a spindle cell pattern. In the present case, the tumor did not show any sarcomatoid changes but did have spindle components with grade 3 nuclear grading. Therefore, the spindle components of the present case may have similar characteristics to sarcomatoid RCC. CD4 and CD8 staining revealed a difference between the tubular and spindle components, and both CD4- and CD8-positve T cells showed greater infiltration in the tubular components than in the spindle components in the resected specimen (Fig. 7, 8).

Transforming growth factor receptor-β (TGF-β) signaling in the tumor microenvironment has been associated with a poor prognosis (22), and transcriptional analyses have suggested that different pathways are enriched in sarcomatoid RCC, particularly TGF-β signaling (23). As a pleiotropic cytokine, TGF-β maintains immune homeostasis through regulation of essentially every cell type of the innate and adaptive immune system. Specifically, TGF-β suppresses the proliferation, differentiation, and effector functions of multiple immune cell types, especially T lymphocytes, and induces the generation of

immunosuppressive cells or phenotypes (24, 25). TGF-β may thus be a factor that caused the weak infiltration of CD4- and CD8-positve T cells in spindle components compared to tubular components.

Conclusion

We reported the first case of MTSCC of the kidney with bone metastases treated with the combination of nivolumab plus ipilimumab therapy. MTSCC of the kidney is a rare subtype of RCC, and no standard therapeutic care has been established for metastatic MTSCC of the kidney. However, the present case suggested that combination immunotherapy might be an effective treatment option for metastatic MTSCC of the kidney. More studies with a larger number of patients with this rare disease are needed.

Declarations

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Availability of date and materials

All date generated or analyzed during this study are included in this published article.

Authors' contributions

All listed authors have approved the manuscript before submission, including the names and order of authors, and all authors receive the submission and all substantive correspondence with editors, as well as the full reviews, verifying that all data, figures, comply with the transparency and reproducibility standards of both the field and journal.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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

Competing interests

The authors declare that they have no conflict of interest for this study.

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Figures

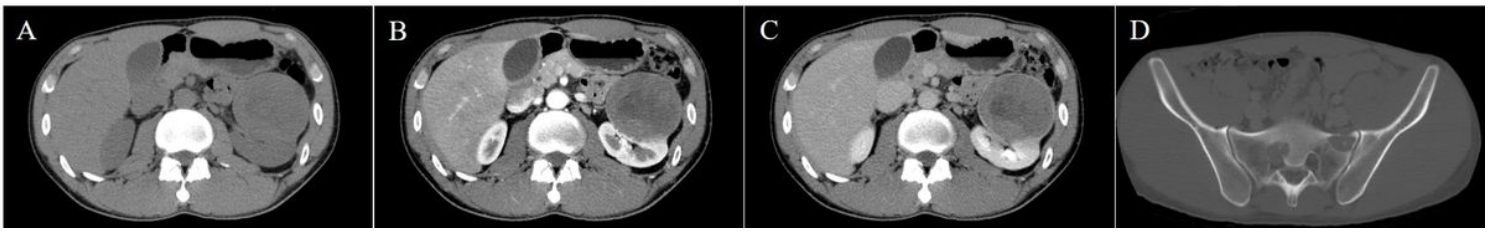

Figure 1

Pretreatment CT findings. (A-C) CT revealed a 72-mm tumor at the upper pole of the left kidney that was well-circumscribed and slightly enhanced heterogeneously in the corticomedullary phase and excretory

phase. (D) Multiple osteolytic changes were confirmed in bone.

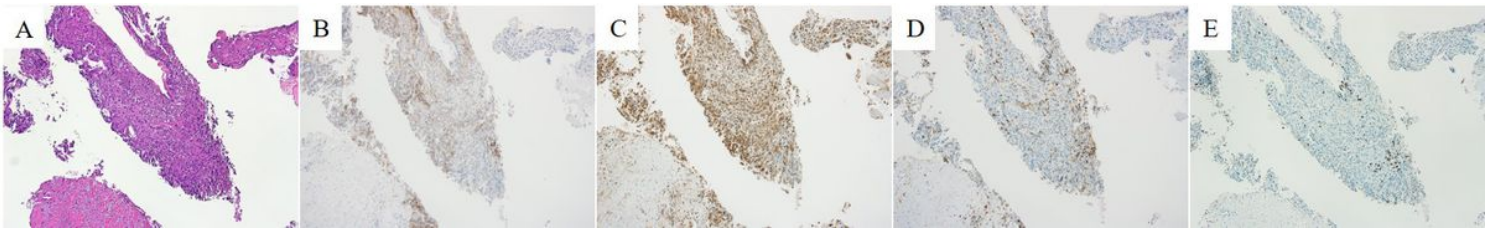

Figure 2

The biopsy of the left renal tumor. (A) Hematoxylin Eosin, (B) programmed cell death ligand-1, (C) cytotoxic T lymphocyte–associated antigen-4, (D) CD4, (E) CD8.

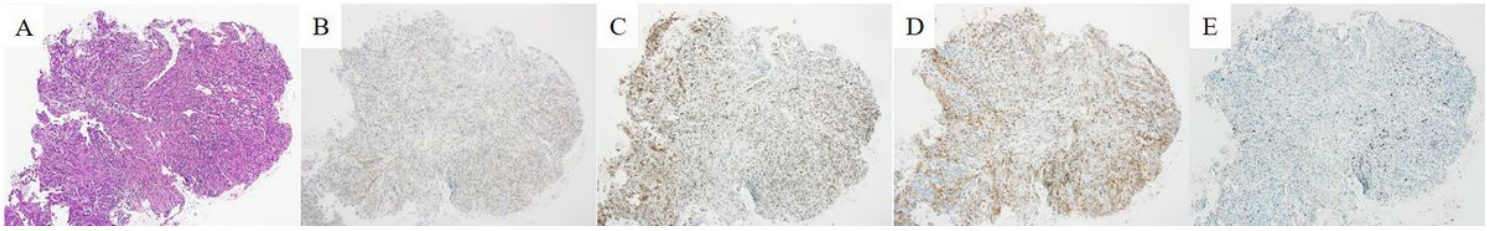

Figure 3

The biopsy of bone metastases. (A) Hematoxylin Eosin, (B) programmed cell death ligand-1, (C) cytotoxic T lymphocyte–associated antigen-4, (D) CD4, (E) CD8.

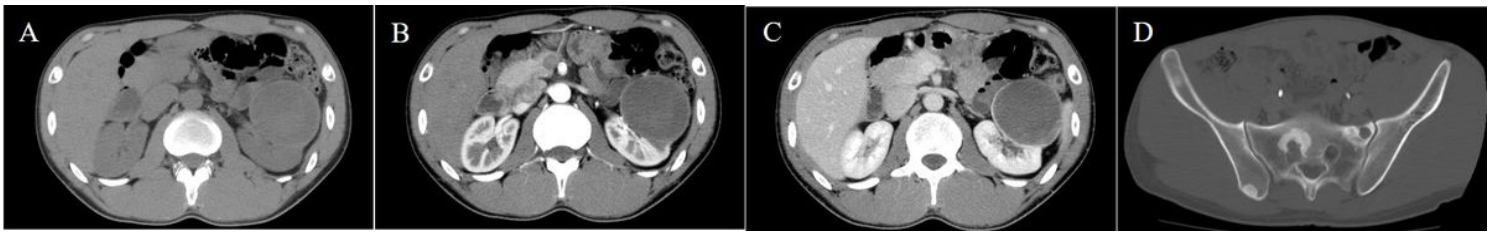

Figure 4

CT after combination therapy of nivolumab plus ipilimumab and eight courses of nivolumab monotherapy. (A-C) CT revealed that the left renal tumor had shrunk slightly, and the non-enhanced area was increased. (D) The osteosclerotic changes in bone metastasis were increased.

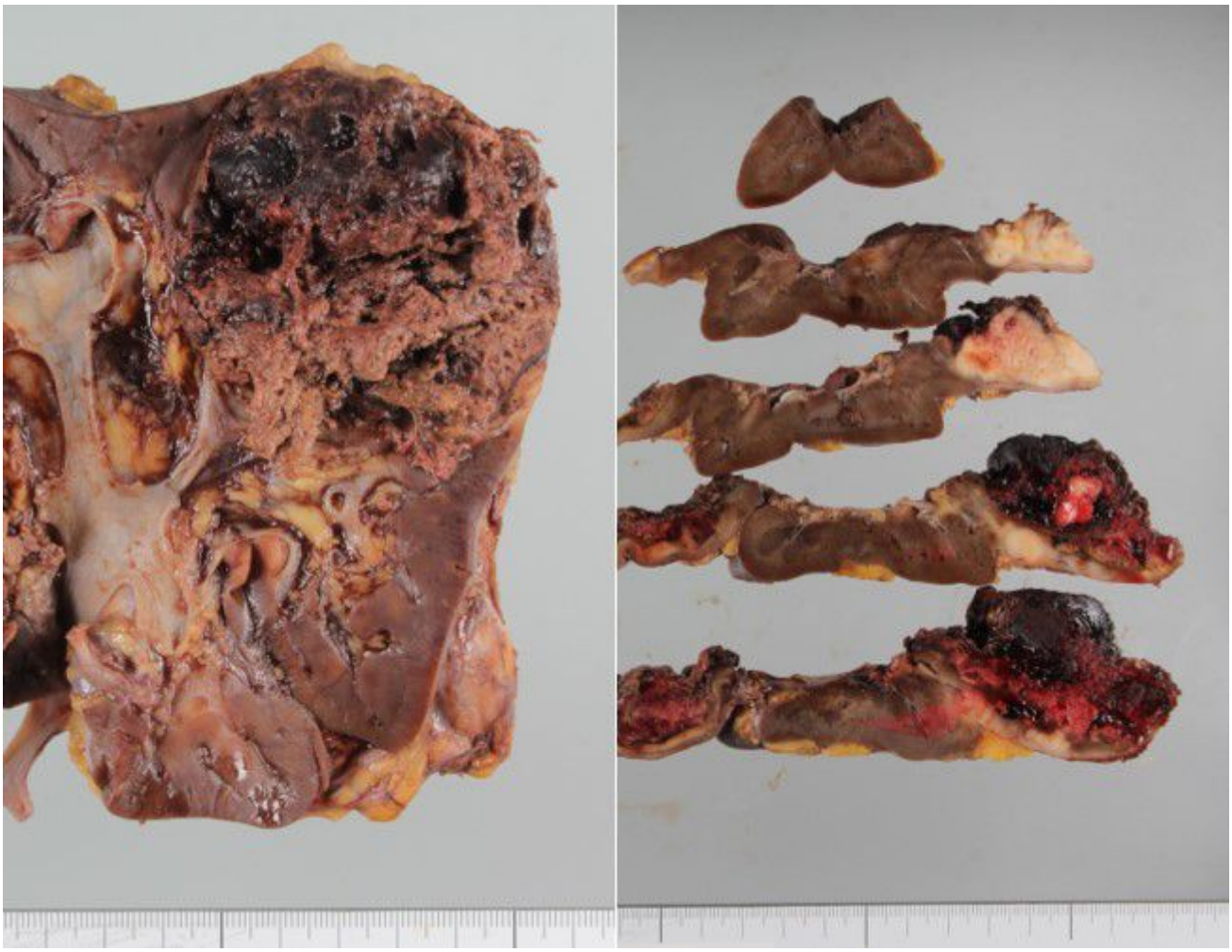

Figure 5

Microscopic findings. The tumor at the upper pole of left kidney was mostly necrotic with hemorrhaging and white-toned solid parts.

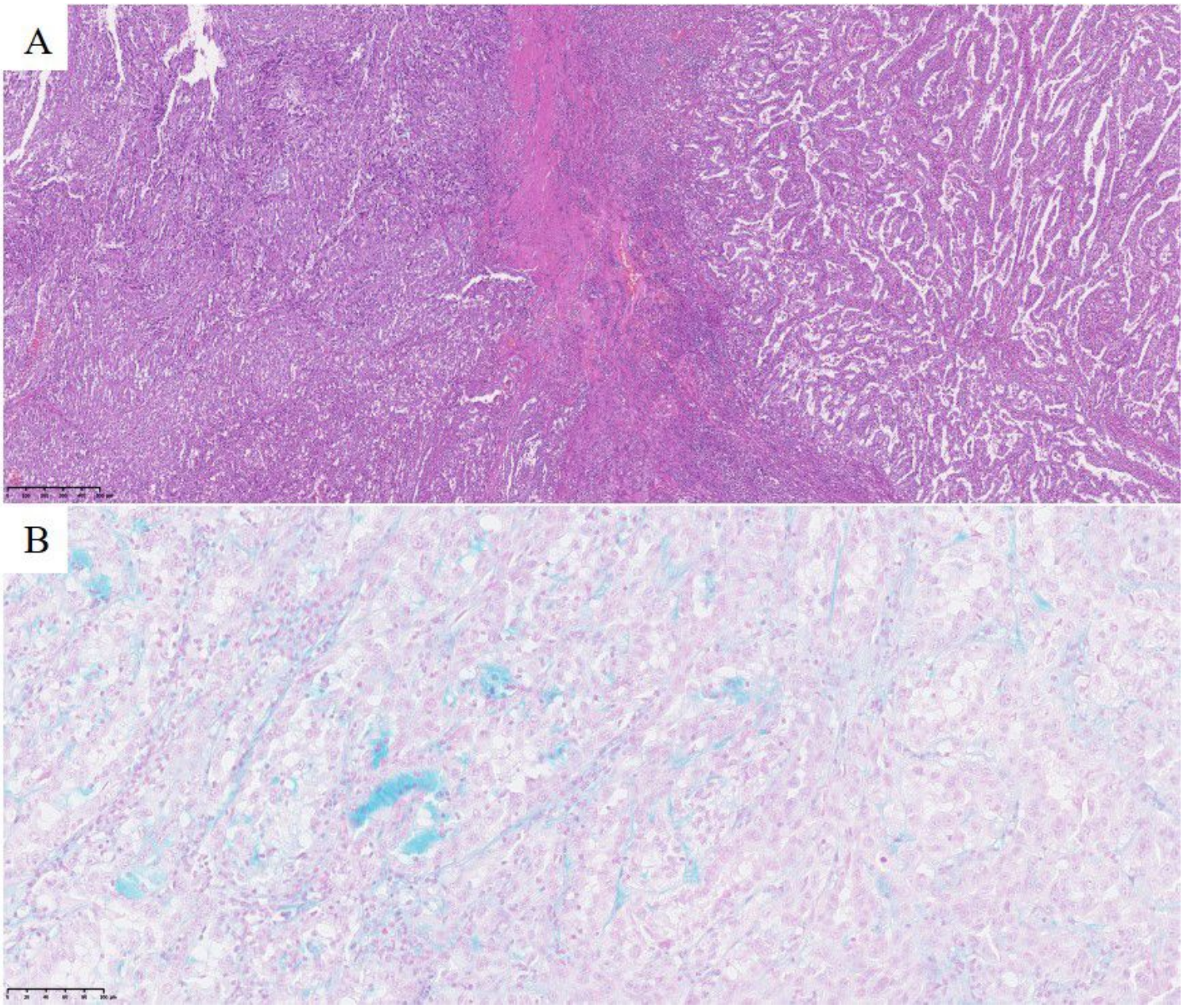

Figure 6

Excised specimen. (A) Hematoxylin Eosin, tubular components on the right side and spindle components on the left side. (B) Alcian blue staining.

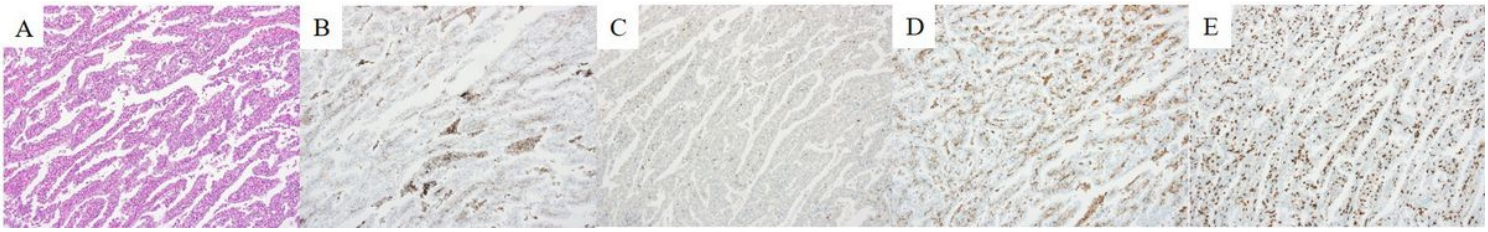

Figure 7

Tubular components. (A) Hematoxylin Eosin, (B) programmed cell death ligand-1, (C) cytotoxic T lymphocyte–associated antigen-4, (D) CD4, (E) CD8.

Figure 8

Spindle components. (A) Hematoxylin Eosin, (B) programmed cell death ligand-1, (C) cytotoxic T lymphocyte–associated antigen-4, (D) CD4, (E) CD8.

Supplementary Files

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- CAREChecklist.pdf