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Difficulty in differential diagnosis for renal cancer with microscopic papillary architecture: overlapped pathological features among papillary renal cell carcinoma (RCC), mutinous tubular and spindle cell carcinoma, and unclassified RCC. Lessons from a Japanese multicenter study

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Abstract

Objectives: In our multicenter study evaluating metastatic papillary renal cell carcinoma (PRCC), 29% of tumors diagnosed as PRCC in collaborative institutes were finally diagnosed as other RCCs under central review. In those tumors, mucinous tubular and spindle cell carcinoma (MTSCC) was the leading histology, followed by unclassified RCC (ucRCC). We focused on those patients with MTSCC or ucRCC.

Methods: We reviewed the processes for the pathological diagnoses of nine tumors and reviewed their clinical features.
Results: All of the MTSCCs and ucRCCs were positive for AMACR, which is frequently positive in PRCC. Mucin was demonstrated in 80% of the MTSCCs, and its presence is important for their diagnoses. One MTSCC was diagnosed as a mucin-poor variant. The presence of spindle cells with low-grade nuclei was suggestive of MTSCC, but the diagnosis of high-grade MTSCC was difficult. Four tumors were diagnosed as ucRCC by histological and immunohistochemical findings. Three of the four tumors were suspicious of ucRCC in the initial review due to atypical findings as PRCC. Sunitinib and interferon-α were effective for one MTSCC patient who survived for >5 years. Two MTSCC patients who were Memorial Sloan-Kettering Cancer Center poor risk had unfavorable prognoses. One patient with mucin-poor MTSCC had an indolent clinical course. Two of four ucRCC patients showed durable stable disease with targeted agents (TAs) and survived >3 years.
Conclusion: Some MTSCC metastases progressed very slowly and poor-risk tumors progressed rapidly. Systemic therapies including TAs showed some efficacies. Some patients who have metastatic ucRCC with microscopic papillary architecture can benefit from TAs.

Key words: metastatic mucinous tubular and spindle cell carcinoma, unclassified renal cell carcinoma, microscopic papillary architecture, immunostainings, clinical outcome, systemic therapy

Introduction

Various kinds of renal cell carcinomas (RCCs) have pathological papillary architecture in their tumor (1). Differential diagnoses of RCCs that show partly papillary architecture are sometimes difficult, and further evaluation by additional histological and immunohistochemical analyses is necessary for pathological diagnosis. We previously performed a Japanese multicenter study evaluating metastatic papillary RCC (PRCC) (2). In that study, 51metastatic RCCs diagnosed as PRCCs in each collaborative institution were reevaluated with hematoxylin–eosin (HE)-stained slides by three central pathologists. In that central review process, only 21 tumors (41.2%) could be diagnosed as PRCCs in the first evaluation, and additional histological analyses and immunostainings were needed for the other tumors. Finally, 15 tumors (29.4%) were diagnosed as other types of RCC. In those tumors, mucinous tubular and spindle cell carcinoma (MTSCC) were the leading histology (five tumors) followed by unclassified RCC (ucRCC) (four tumors). MTSCC has an intimate relationship with PRCC, including morphological and immunohistochemical overwrapping (1). Therefore, differential diagnosis of these two is sometimes challenging. Standard medical treatment for metastatic MTSCC has not yet been established. Only small case series (3,4) and case reports (5–14) have been reported. To determine effective medical treatments for metastatic MTSCC, more cases with metastatic MTSCC should be collected for multicenter study. ucRCC appears to be miscellaneous RCCs for which a pathological diagnosis could not be determined in various histological and immunohistochemical evaluations. However, the ucRCCs in our study are specially characterized by having microscopic papillary architecture and were once diagnosed as PRCC. This kind of ucRCCs with papillary architecture may have resembled clinical courses of PRCC and may respond to common medical treatments.

In the present study, we focused on nine patients whose tumors were reclassified as MTSCC or ucRCC in the previous multicenter study in which patients with metastatic PRCC (mPRCC) were evaluated (2). We reviewed the processes of each pathological diagnosis made by central pathologists and also reviewed their clinical features.

Methods

Patients and methods

In this multicenter study, 51 patients whose tumors were diagnosed as mPRCC were enrolled (2). Among these tumors, 15 tumors (29.4%) were finally diagnosed as other histological types (2). Pathological slides of enrolled patients were evaluated by three central pathologists (S. M., N. K. and Y. N.) who were board certified and specialized in genitourinary malignancies. The process of central pathological review was described previously (2). Briefly, when a pathological diagnosis could not be determined in the first evaluation using HE-stained slides, additionally histological and immunohistochemical analyses were performed by using key paraffin-embedded sections that were freshly prepared (2). After central pathologists reviewed the HE-stained slides, additional immunostained slides and patients' clinical information, the final diagnoses were made according to the recent WHO classification (1). The 15 tumors consisted of five MTSCC, four ucRCC and other RCCs including translocation RCC, collecting duct carcinoma, and clear cell RCC. In the present study, we focused on patients with MTSCC and those with ucRCC. The additional immunohistochemical analyses are shown in Table 1. Also, clinical information, treatments and outcomes of the nine cases were reviewed (Table 2). When any medical treatments (cytokine, targeted therapy and chemotherapy) were administered, the patients were generally followed up on every 2–4 weeks thereafter. Computerized tomography (CT) was generally performed every 2–3 months, and additional CTs, MRIs and elective bone scans were performed when clinically indicated. The Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification was determined within a month prior to the administration of any treatment for metastasis. This study was approved by the institutional review boards of the participating institutions.

Evaluation

Clinical backgrounds, pathological findings, any treatments and treatment outcomes were collected from collaborative institutions. Tumor responses (best response) were defined according to the

Table 1. Processes of central pathological evaluation for patients with rare RCCs in final pathological diagnoses

Case	Initial diagnoses at each institution	Final diagnosis by central review	Differential diagnoses in the initial central review	Results of additional IHC	Important information
1	Papillary, type?	MTSCC (mucin-poor type)	Type 1 or 2 PRCC or MTSCC	Alcian blue (−), AMACR (+), CD10 (partially positive), CK7 (+), TFE3 (−)	Spindle cell with low NG (atypical for PRCC)
2	Papillary, type 2	MTSCC	Type 2 PRCC or CDC or MTSCC	Alcian blue (+), CK7 (−), AMACR (+), CD10 (−), 34βE12 (partially positive)	Relatively uniform small tumor cells
3	Papillary, type?	MTSCC	Type 2 PRCC with SC or MTSCC	Alcian blue (+), AMACR (+), cathepsin K (−), CD10 (−), CK7 (−), CK19 (−), melanosome (−), TFE3 (−), RCC-Ma (partially positive)	Spindle cell with low NG, AMACR (diffusely positive)
4	Papillary, type 2	MTSCC	MTSCC (high grade) or CDC	Alcian blue (+), AMACR (+), CD10 (+), p63 (−), 34βE12 (−)	Abundant mucus in interstitium
5	Papillary, type 2	MTSCC (high grade)	MTSCC, probably	Alcian blue (+), AMACR (+), CK7 (+)	Short spindle cells are intermixed
6	Papillary, type 2 (with SC)	Unclassified (diffuse SC)	Unclassified or ccRCC or MTSCC (diffuse SC)	AMACR (+), CA9 (−), CK7 (−), TFE3 (−)	Atypical finding as PRCC, solid growth, diffuse SC with high NG
7	Papillary, type 2	Unclassified	ChRCC or unclassified RCC	AMACR (+), CK7(−), c-kit (partially positive),	Atypical finding as PRCC, (HE and IHC), solid growth with high NG
8	Papillary, type 2 (with SC)	Unclassified	Type 2 PRCC with SC or MTSCC or Xp11.2 tRCC	Alcian blue (−), AMACR (+), cathepsin K (−), CD10(−), RCC Ma (+), CK 7 (+), CK19 (partially positive), melanosome (−), TFE3 (−)	Micropapillary growth (partly), presence of clear cells (partly), no mucin in interstitium
9	Papillary, type 2	Unclassified	Unclassified RCC?	AMACR (diffusely positive), CA9 (diffusely positive, non-specific?), CK7 (−), c-kit (−)	Atypical finding as PRCC (HE and IHC), solid growth

AMACR: α-methylacyl CoA-racemace, CDC: collecting duct carcinoma, ChRCC: chromophobe renal cell carcinoma, CK: cytokeratin, HE: hematoxylin–eosin, IHC: immunohistochemistry, MTSCC: mucinous tubular and spindle spindle cell carcinoma, NG: nucleolar grade, PRCC: papillary renal cell carcinoma, RCC Ma: renal cell carcinoma marker, SC: sarcomatoid change, tRCC: translocation-associated RCC.

Response Evaluation Criteria in Solid Tumor (RECIST) v1.1. The MSKCC risk model includes five parameters (15). The survival duration was defined as the time from the appearance of metastasis to the date of death or was censored at the last follow-up. When patients already had metastasis in the initial presentation, the survival duration was calculated from the time of nephrectomy.

Results

Process of central review

After central review, various histological and immunohistochemical analyses were added (Table 1). Five MTSCCs were all positive forα-methyl acyl CoA racemase (AMACR). Of the five MTSCCs, mucin was demonstrated in the interstitium in four tumors by alcian-blue staining. In case 1, both AMACR and CK7 stainings were positive and mucin was not demonstrated. PRCC with sarcomatoid change (SC) was once suspected because of the presence of spindle cells. However, the spindle cells had a low nucleolar grade, unlike the representative SC. As the result of a conference held by three central pathologists, the tumor was diagnosed as a mucin-poor type MTSCC. A typical MTSCC case (case 3) is shown in Fig. 1. Differential diagnoses after the first evaluation were type 2 PRCC with SC or MTSCC. Because the nucleolar grade of the tumor cells was low and mucin was demonstrated in the stroma, the tumor was diagnosed as MTSCC.

Four patients with ucRCC that had pathological papillary architecture are shown in Table 1 (cases 6–9). Various types of RCCs including MTSCC, chromophobe RCC, Xp11.2 translocation-associated RCC and clear cell RCC were diagnostic candidates of those four tumors. All four tumors were positive for AMACR. Although various histological and immunohistochemical analyses were done for them, these tumors could not be categorized as any RCCs and were diagnosed as ucRCC. In three of the four tumors, PRCC was unlikely in the first evaluation according to the HE-stained slides (cases 6, 7, 9). In particular, in case 9, ucRCC was already highly suspected in the first evaluation. The typical process of pathological diagnosis (case 8) is shown in Fig. 2. A papillary component (Fig. 2A) and spindle cells (Fig. 2B) were present, and PRCC with SC was first suspected. The tumor was positive for

Table 2. Clinical course of the nine patients with MTSCC or unclassified RCC

Case	Age/gender	Final diagnosis by central review	MSKCC risk	Metastasis	Operation (year/month)	Systemic treatment (BR, duration)	Local treatment	Prognosis**
1	54/M	MTSCC mucin-poor type	Inter.	LU*	RNx (2001/07)	IFN, IL2, So, EV, Su, Tem (no response to any treatment)	No	127.9 mo, A
2	75/F	MTSCC	Fav.	Retroperitoneum (14 mo after RNx)	RNx (2009/08)	Tem (SD, 3.7 mo), Su (SD, 5.5 mo), EV (AE), Axi (AE)	No	27.8 mo, D
3	61/F	MTSCC	Poor	LU*	RNx+ THB (T3c) (2004/06)	IFN (PD), IL2 (PD)	No	14.7 mo, D
4	72/M	MTSCC	Inter.	LU*	RNx + LND (2008/05)	IFN (SD, 36.6 mo), Su (SD, 11.3 mo) Axi (PD)	No	66.3 mo, D
5	70/M	MTSCC (high grade)	Poor	LU, LN (6 mo after LPN)	LPN (2012/11)	Tem (PD)	RT (LN)	3.7 mo, D
6	80/M	Unclassified (mainly SC)	Poor	Bone, LU (4 mo after RNx)	RNx + THB (2008/08)	Su [1.8 mo (AE)]	RT (bone)	8.9 mo, D
7	38/M	Unclassified (SC+)	Inter.	LN* Bone (1 mo after RNx)	RNx + LND (2011/06)	Tem (PD), Su (SD, 5.6 mo), Axi (SD, 22.1 mo)#	Posterior spine fusion	37.7 mo, D
8	62/M	Unclassified	Inter.	LN*, adrenal*, skin*	RNx (2002/11)	IFN (PD)	Metx (skin)	16 mo, D
9	66/F	Unclassified	Inter.	Bone*, LU*	LRN (2011/08)	Su (SD, 16.1 mo), Tem (SD, 21.4 mo)	RT (pubis, spine)	43.8 mo, D

*at first visit

**from the appearance of metastasis

#Axitinib still continued.

A: alive, AE: stopped by adverse event, Axi: axitinib, BR: best response, D: dead, EV: everolimus, Fav.: favorable, IFN: interferon, Inter.: intermediate, IL-2: interleukin-2, LN: lymph node, MSKCC: Memorial Slon Kettering Cancer Center, MTSCC: mucinous tubular and spindle cell carcinoma, PD: progressive disease, RCC: renal cell carcinoma, RT: radiation therapy, SC: sarcomatoid change, Su: sunitinib, Tem: temsirolimus, THB: thrombectomy.

AMACR and CK7 (Fig. 2C and D). However, there were also histological findings that were atypical for PRCC (Fig. 2E and F). MTSCC was thus suspected, but the alcian-blue staining was negative (not shown). Finally, the tumor was diagnosed as ucRCC.

Clinical characteristics and outcomes of the nine cases

A patient with mucin-poor MTSCC (case 1) showed a quite rare clinical course. Cytokine therapy, targeted therapies and cytotoxic agent (S-1) were used for lung metastases. The tumor did not respond to any medical treatments. However, the patient was alive for more than 10 years after nephrectomy because the metastatic lesions progressed very slowly. Case 2 had stable disease (SD) for several months with temsirolimus and sunitinib. Case 3 had a clinical T3c tumor with lung metastases and was classified as MSKCC poor risk. The patient was treated prior to the era of molecular targeted therapy and the tumor did not respond to cytokine therapies. The patient was dead 14.7 months after nephrectomy. Case 4 had lung metastases and showed durable SD (36.6 months) with interferon- α (IFNα) and showed SD (11.3 months) with sunitinib. The tumor in case 5 (high grade MTSCC) did not respond to temsirolimus, progressed rapidly, and he was soon dead.

The clinical courses of the four patients with ucRCC are summarized in Table 2. Case 6 was an MSKCC poor-risk patient, and sunitinib was not effective. Radiotherapy to bone metastasis was done, but the patient was dead 8.9 months after metastases. Case 7 (intermediate risk) had lymph node and bone metastases. Temsirolimus was not effective, but this case showed SD with sunitinib (5.6 months) and durable SD with axitinib (22.1 months). Case 8 had multiple metastases (lymph node, adrenal and skin) in the initial presentation. IFNα was not effective, and the patient was dead after 16 months after nephrectomy. Case 9 (intermediate risk) had bone and lung metastases and had durable SD with sunitinib (16.1 months) and temsirolimus (21.4 months).

Discussion

In our multicenter study evaluating mPRCC, about 30% of enrolled tumors that had been diagnosed as PRCC in each institution were finally diagnosed as other histological types under central pathological review (2). Because several RCCs such as PRCC, clear cell papillary RCC, collecting duct carcinoma, translocation RCC, MTSCC and ucRCC frequently have microscopic papillary

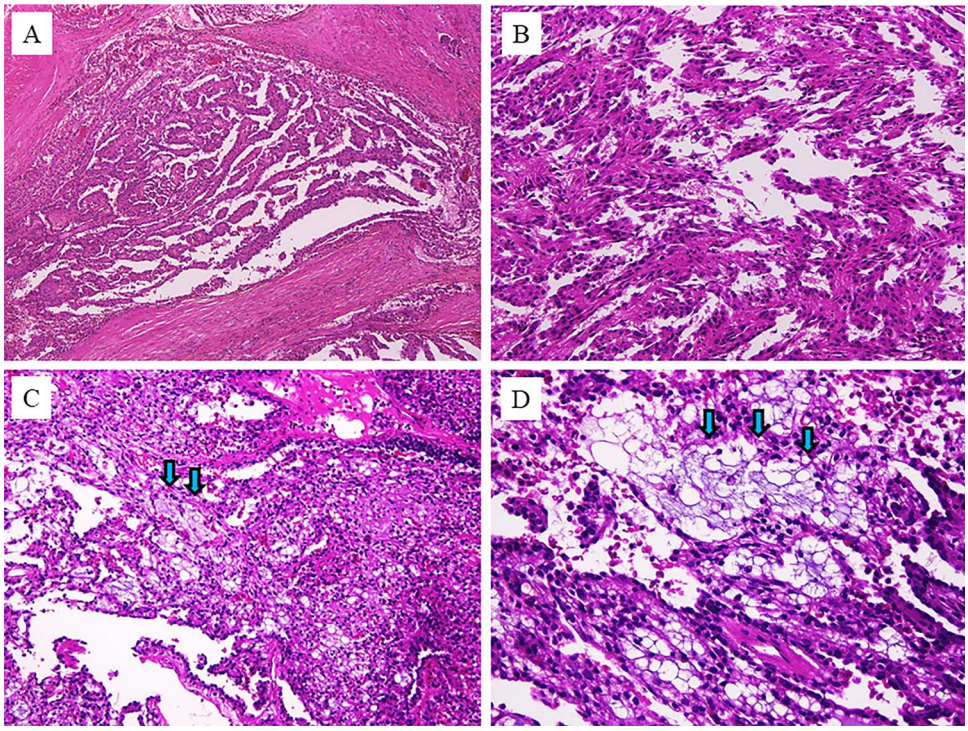

Figure 1 The tumor in case 3 was suggestive of type 2 PRCC with sarcomatoid change at initial central review. A: papillary structure in the tumor. B: Spindle cells had low nuclear grade, unlike representative sarcomatoid change. C and D: Mucus was demonstrated in the stroma of the tumor by alcian-blue staining. Then, the tumor was diagnosed as MTSCC.

architecture, pathological diagnoses are sometimes difficult. In particular, the results of histological and immunohistochemical analyses are likely to be overlapped among PRCC, MTSCC and ucRCC (1). In the present study, pathological diagnoses could not be determined for 30 of the 51 tumors (59%) in the first evaluation using HE-stained slides. When pathological diagnosis cannot be reached with HE-stained slides, specific histological and immunohistochemical analyses should be added based on the basis of the differential diagnoses in the first evaluation. Then, pathological diagnosis should be determined by re-evaluating HE-stained slides, immunostained slides, macroscopic findings of tumors and clinical information (age, gender, sites of metastases, etc.) on the basis of careful discussion by pathologists. As shown in Figs 1 and 2, (cases 3 and 8) various histological analyses such as alcian-blue staining and immunostainings for AMACR and CK7 should be done to determine pathological diagnosis. In addition to immunohistochemical analyses, atypical morphologies in HE-stained slides are suggestive of other histological types than PRCC. It is sometimes difficult to differentiate MTSCC from PRCC with SC. In such cases, spindle cells with a low nucleolar grade are suggestive of MTSCC. Also, atypical findings such as alveolar structures of clear cells and nests of micropapillary structures (Fig. 2E and F) are suggestive of histological types except PRCC. In addition, PRCC and MTSCC may be distinguishable by evaluating the presence of trisomy for chromosomes 7 and 17 by fluorescence *in situ* hybridization (16).

The therapeutic strategy has not been established for metastatic MTSCC. Only case reports (5–14) and case series (3,4) have been reported regarding the treatment of metastatic MTSCC. In those reports, targeted agents (TAs) (4,5,7,12) and nivolumab (14,17) showed some efficacies. Among TAs, sunitinib showed a prolonged response (4) and SD for >6 months (7) in case reports. Also, Takahashi et al. reported a patient with metastatic MTSCC whose lung and bone metastases responded completely to third-line nivolumab (14). In our series, the clinical courses of the five patients with metastatic MTSCC were various. MTSCC was originally reported as a rare histological type of RCC with low malignant potential (1,18). However, it was found that some MTSCC cases rapidly progressed (8–11). In case 1, the lung metastases did not respond to any medical treatments. However, the metastases progressed very slowly, and the patient was alive for more than 10 years. The patient showed a quite unusual clinical course for a metastatic disease. The indolent-progressing metastatic tumor may be one of the typical phenotypes of metastatic MTSCC. Kenny et al. reported in a case series a patient with metastatic MTSCC whose metastases progressed despite systemic therapy at 26.7 months from the date of diagnosis and who died at 64.7 months (3). An MTSCC patient with indolent-progressing metastases was also reported in another report (13). Case 1 was diagnosed with mucin-poor type MTSCC. Mucin-poor variants have been reported previously (9,11). Although the metastases in case 1 progressed very slowly, previously reported patients with mucin-poor MTSCC showed an aggressive clinical course (9,11). Case 2 had SD within 6 months with temsirolimus and sunitinib. The metastatic site of case 4 was only the lungs and the patient had durable SD with IFNα (36.6 months) and SD with sunitinib (11.3 months). Cytokine therapy and targeted therapy were effective in that case. The poor-risk patient with high-grade MTSCC (case 5) progressed rapidly. Such aggressive type of high-grade MTSCC was reported previously (10). In that report, multiple metastases appeared 5 months after nephrectomy, and the patient was dead suddenly 12 days after sunitinib initiation. From

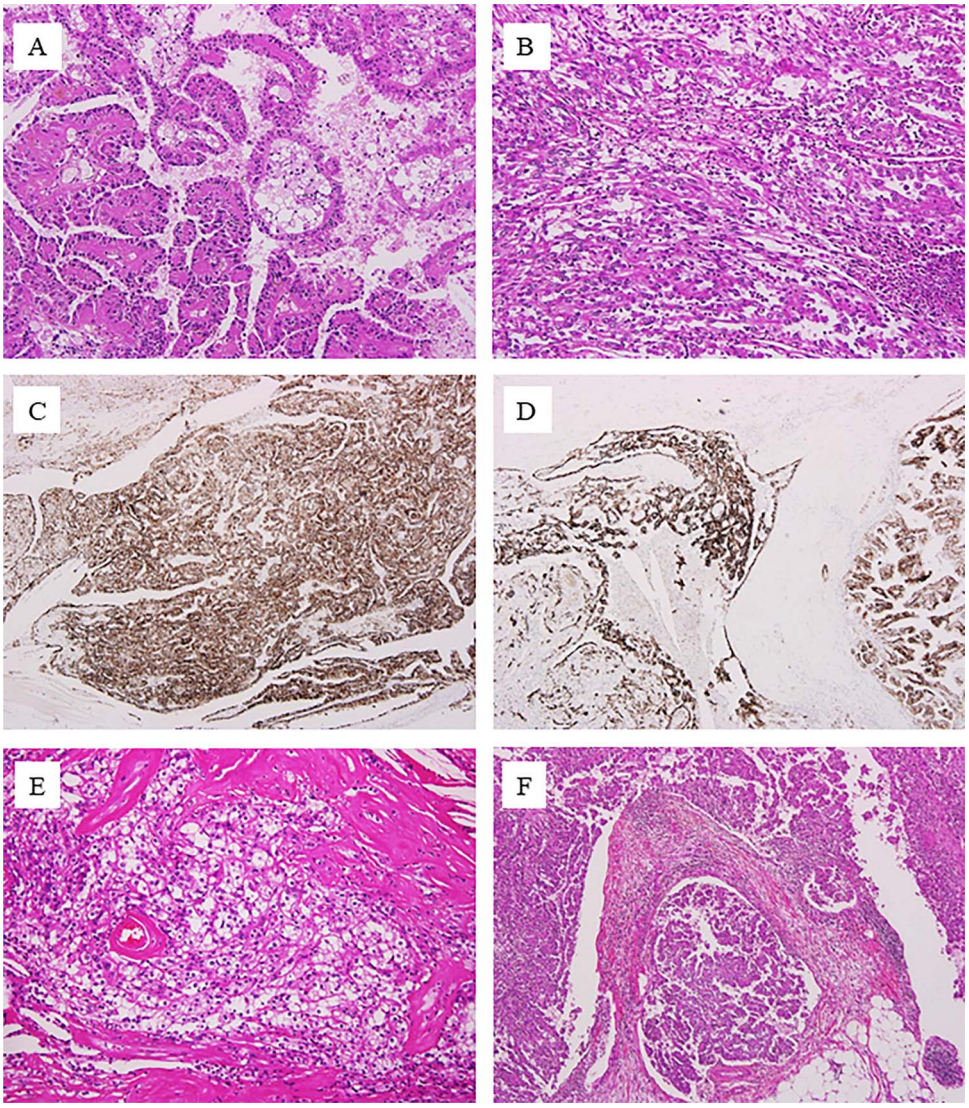

Figure 2 A: Papillary component of the unclassified RCC (case 8). The tumor was suggestive of PRCC with high nuclear grade at initial central review. B: There were high-grade spindle cells in the tumor, suggesting type 2 PRCC with high nuclear grade. C and D: The tumor was positive for AMACR (C) and cytokeratin 7 (D). These immunopositivities were suggestive of PRCC and MTSCC. E: There were alveolar structures with clear cells, which were atypical as PRCC. F: There were nests of micropapillary structure, which were also atypical as PRCC. A-F: The tumor was suggestive of high-grade MTSCC. However, alcian-blue staining was negative (not shown). The tumor was diagnosed as unclassified RCC because of the absence of mucus in the interstitium.

the results of our cases and previously reported cases, it appears to be a fact that targeted therapy, cytokine therapy and immune-checkpoint inhibitors are sometimes effective for metastatic MTSCC. Because a therapeutic strategy has not yet been established due to its rarity, multicenter study evaluating systemic therapies for MTSCC is needed. In addition to the systemic therapy, metastasectomy may have some efficacy similar to the case for clear cell RCC. Kubota et al. reported a surgical CR case (T3bN0M0 MTSCC) who underwent nephrectomy and thrombectomy and two metastasectomies at 2 and 5 years after nephrectomy and survived without disease for more than 10 years after nephrectomy (13).

Our ucRCC cases are characterized by having microscopic papillary architecture. This characteristic leads us to the idea that effective medical treatment for metastatic ucRCC with papillary architecture might be similar to that for mPRCC. Sunitinib and axitinib were effective in case 7, and sunitinib and temsirolimus showed durable SD in case 9. These two cases suggested that targeted therapies might be effective for metastatic ucRCC with microscopic papillary architecture. Our previous study evaluating mPRCC showed the clinical efficacy of tyrosine kinase inhibitors (2). Clinical efficacy of targeted therapies for metastatic ucRCC has been shown in clinical trials (19–21). In a phase II trial with sunitinib for non-clear cell RCC, the disease control rate was 63% for patients with ucRCC and the median PFS was 3.2 months (19). In a Korean phase II trial evaluating the clinical activity of sunitinib for non-clear cell RCC, three of five patients with ucRCC had PR and two of those had SD (20). In an ASPEN trial in which the clinical efficacy of sunitinib and that of everolimus for non-clear cell RCC were compared, the mPFS was 11.5 months with sunitinib and 5.7 months with everolimus (21). The immunoreactivities of the tumor in case 8 were overlapped with those of typical MTSCC, but mucin was not demonstrated by alcian-blue staining. Case 8 was treated prior to targeted era and

the tumor showed no efficacy to IFNα. From the results of our cases, targeted therapies, especially sunitinib, might be the treatment of choice for the treatment of metastatic ucRCC with microscopic papillary architecture. Immune-checkpoint inhibitors were not used in our cases because these cases were treated before the era of immunotherapy. A multicenter retrospective study evaluating the clinical efficacy of nivolumab for non-clear cell RCC included 14 patients with ucRCC (22). Four of the 14 patients showed a response and 3 of them showed SD. Immune-checkpoint inhibitor appear to be a viable option for ucRCC and further study will be necessary.

This study has limitations. First, this study is a retrospective study (case series) with a small number of patients. This small number made it impossible for us to perform statistical analysis. Multicenter trials will be needed to evaluate a larger number of patients with metastatic MTSCC and ucRCC to establish treatment strategies for those rare RCCs. Second, metastatic MTSCCs and ucRCCs in this study were selected tumors that had microscopic papillary architecture and were once diagnosed as PRCC at collaborative institutions. Therefore, clinical features and responses to systemic therapies of our patients cannot be generalized as those of whole patients with metastatic MTSCC or ucRCC. The valuable point of the present study is that we showed the difficulty in determining the pathological diagnosis of RCCs with microscopic papillary architecture and the necessity of additional histological and immunohistochemical evaluations.

Conclusions

It is sometimes difficult to distinguish MTSCC and ucRCC with microscopic papillary architecture from PRCC. When pathological diagnosis cannot be determined with HE-stained slides, additional histological and immunohistochemical analyses are needed. In our patients with metastatic MTSCC, some tumors grow very slowly, and some poor-risk or high-grade tumors progressed rapidly. Systemic therapies including targeted therapies were sometimes effective for MTSCC. However, multicenter trials with a large number of patients must be done to establish a treatment strategy for this rare RCC. Some metastatic ucRCC with microscopic papillary architecture can respond to the targeted therapies.

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Conflict of interest statement

Naoya Masumori MD reports receiving research funding from Ono. Tsunenori Kondo MD reports receiving honoraria from Bayer, Novartis and Pfizer during the conduct of the study. Masatoshi Eto MD reports receiving research funding and honoraria from Novartis, Ono and Pfizer and honoraria from Bayer, Bristol-Myers Squibb during the conduct of the study. Yoshihiko Tomita MD reports receiving research funding and honoraria from Astellas, Ono and Pfizer; research founding from AstraZeneca and honoraria from Bristol-Myers Squibb and Novartis and consultancy fees from Novartis, Ono; and Taiho during the conduct of the study. Hideyasu Matsuyama MD reports receiving honoraria from Bayer, Ono and Pfizer during the conduct of the study. Hayakazu Nakazawa MD reports receiving honoraria from Bayer, Novartis and Pfizer during the conduct of the study. Mototsugu Oya MD reports receiving research funding; and honoraria from Novartis, Ono and Pfizer and honoraria from Bayer during the conduct of the study. Go Kimura MD reports receiving research funding and honoraria from Ono, Bristol-Myers Squibb and Bayer, and honoraria from Novartis and Pfizer during the conduct of the study; Nobuo Shinohara MD reports receiving honoraria from Novartis and Pfizer and is an advisor for Ono during the conduct of the study. Other authors declare that they have no conflict of interest. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee in each institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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