Metachronous primary non-small cell lung cancer and mucinous tubular and spindle cell carcinoma of the left kidney: A case report

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Abstract. Multiple primary malignant tumors (MPMTs) refer to two or more independent malignancies occurring at different anatomical sites. The present study reports the first documented case of metachronous primary lung adenocarcinoma and renal mucinous tubular and spindle cell carcinoma (MTSCC). A 69-year-old man underwent a radical lobectomy for stage IIB (pT2aN1M0) lung adenocarcinoma followed by adjuvant chemotherapy. A routine 10-month postoperative follow-up computed tomography scan revealed an ill-defined left renal mass. Subsequently, a partial nephrectomy was performed. Histopathological examination confirmed MTSCC. No recurrence was observed after 3 years of surveillance. The present study is, to the best of our knowledge, the first to report the association between lung adenocarcinoma and MTSCC, which highlights the necessity to consider a new primary malignancy in cancer survivors with new lesions. The present case highlights the critical role of integrated histopathological and immunohistochemical evaluation in distinguishing rare primary cancers, such as MTSCC, from metastasis, thus guiding appropriate therapy.

Introduction

Advances in diagnostics, treatment and patient longevity have contributed to the increasing incidence of multiple primary malignant tumors (MPMTs), defined as two or more histologically distinct malignancies in a single individual (1). MPMTs are classified as synchronous or metachronous based on the timing of diagnosis, with the latter often being associated with a poorer prognosis. First described in the late 19th century, formal diagnostic criteria for MPMTs were established by Warren and Gates (2) in 1932 and require each tumor to be: i) Pathologically malignant, ii) histologically distinct and iii) not representing metastasis of the other tumor. Malignancies diagnosed within a 6-month interval are considered synchronous (2). The reported incidence of MPMTs ranges from 0.52 to 11.7%, with a higher prevalence in men >50 years old, and the most common combination is adenocarcinoma and squamous cell carcinoma (3). Established risk factors include smoking and heavy alcohol intake (4,5). In addition, patients with MPMT may have a family history of cancer, while other patients are sporadic and may possess DNA mismatch repair gene mutations (6). The diagnosis of MPMTs relies on pathological, histological and immunohistochemical examinations, although no standardized treatment guidelines are available at present. Due to the current lack of standardized treatment guidelines, management is individualized and based on tumor pathology, stage and patient tolerance, ranging from radical to palliative intent.

MTSCC of the kidney is an extremely rare malignant epithelial tumor of the kidney, accounting for <1% of all primary renal tumors (7). Recognized as a distinct entity in the 2004 World Health Organization (WHO) classification (8), MTSCC predominantly affects middle-aged and elderly patients (mean age, ~58 years) and exhibits a significant female predominance (male:female ratio, ~1:3) (9). Characteristic histopathology involves bland spindle cells and tubular structures within a mucinous stroma, with a typical immunophenotype [positive for cytokeratin (CK)7, α-methylacyl-CoA racemase and E-cadherin, and usually negative for high-molecular-weight CKs] (9). Most cases follow an indolent course, and nephron-sparing surgery is often curative (10). However, a minority of patients exhibit aggressive features (such as sarcomatoid transformation and metastasis), which are associated with complex cytogenetic abnormalities (such as multiple chromosome losses) and specific gene deletions (such as *CDKN2A*/*2B*) (11,12). Comprehensive pathological evaluation supplemented by immunohistochemistry and molecular analysis is therefore crucial for an accurate diagnosis and prognosis.

To the best of our knowledge, the present case represents the first documented occurrence of metachronous primary lung adenocarcinoma and renal MTSCC. Although histologically

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distinct, potentially shared pathophysiological mechanisms warrant further consideration and may include: i) Common environmental carcinogen exposure (for example, tobacco smoke, a known risk factor for both lung and some renal carcinomas) (13,14); ii) shared genetic susceptibility, such as underlying germline mutations in cancer predisposition genes or age-related genomic instability, which could facilitate the development of independent primaries (15); and iii) altered immune surveillance in the context of aging and previous oncological treatment (16,17). Positioning this case within the broader literature relating to MPMT emphasizes the unique nature of the present patient. Unlike more common combinations (such as dual aerodigestive tract carcinomas) (18), the concurrence of a pulmonary adenocarcinoma with a rare renal subtype such as MTSCC is exceptional. This highlights the diverse spectrum of MPMTs, reinforces the critical need for meticulous pathological workup to exclude metastasis, and contributes to a more nuanced understanding of the etiological and clinical landscape of multiple primary cancers.

Case report

A 69-year-old man first presented to The Second Hospital of Lanzhou University (Lanzhou, China) in June 2021 with a chronic cough but without dyspnea for 2 months, and with no history of pulmonary disease. The patient had smoked 15 cigarettes daily for 43 years and had not experienced recent weight loss. Throughout the 2-month period, the patient had maintained a good mental status and a clear consciousness, with appetite being unaffected and sleep being undisturbed. Normal bowel movements were noted, with no symptoms of urinary frequency, urgency, pain or hematuria. A physical examination indicated normal skin and conjunctiva, clear lung breath sounds, no tenderness or rebound tenderness in the abdomen, painless percussion over the kidney area and no lower limb swelling. The patient had been diagnosed with depression 3 years previously and had no other surgical or traumatic history. Computed tomography (CT) revealed a mass in the dorsal segment of the lower lobe of the right lung, measuring ~3.3x2.6x2.5 cm, along with enlargement of the mediastinal and hilar lymph nodes (Fig. 1). Additional imaging, including contrast-enhanced abdominal CT, magnetic resonance imaging (MRI) of the brain and a bone scan, revealed no abnormalities. Based on these findings, the patient was clinically staged as stage IB (cT2aN0M0), according to the TNM classification system (19).

Analysis of tumor markers was indicative of primary NSCLC. Tumor biomarker profiling demonstrated notable increases in carcinoembryonic antigen (1,021.2 ng/ml; reference value, <4.7 ng/ml) levels, whereas routine hematological, coagulation and metabolic panels were normal. Subsequently, the patient underwent a right lower lobectomy. Postoperative pathology identified the tumor as lung invasive adenocarcinoma (Fig. 2) (20,21); the tumor was predominantly solid and cribriform, with components of tumor thrombus, micropapillary type and acinar structures. In addition, >90% of the tumor was high-grade. The size of the tumor was revised to 3.5x3.0x2.8 cm, with no invasion of the visceral pleura, or the bronchial and vascular stumps. There was no lymph node metastasis, with the exception of node number 12. Immunohistochemistry was positive for thyroid transcription factor-1 (TTF-1) and NapsinA, but negative for p40 and CK5/6. The Ki-67 index was 40%. The final postoperative stage was classified as T2aN1M0, stage IIB.

Tumor tissue was sent for next-generation sequencing-based targeted genomic profiling (OrigiMed; Zhiben Medical Technology Co., Ltd.) and revealed a missense mutation in TP53 exon 6, negative PD-L1 expression (tumor proportion score <1%) and a tumor mutational burden of 8.15 Mut/MB. The diagnosis was duly confirmed as adenocarcinoma. According to the 2022 Chinese Society of Clinical Oncology Guidelines (22), The patient was initiated on combination chemotherapy with docetaxel (75 mg/m^2) and nedaplatin (100 mg/m^2) administered on day 1 of a 21-day cycle. The patient completed four cycles and tolerated treatment well.

The plan post-chemotherapy was to perform enhanced chest and abdominal CT scans every 3 months for 1 year to assess the patient's condition. A CT scan at 3 months post-chemotherapy revealed a pulmonary artery embolism in the right upper lobe, and color Doppler ultrasound of the lower extremities revealed a thrombus in the right calf muscle vein (Fig. 3). Oral rivaroxaban (20 mg once daily) was administered for anticoagulant therapy. After 3 months of anticoagulation therapy, the pulmonary embolism had resolved.

After a disease-free interval of ~9 months, enhanced abdominal CT scans revealed a round isodense lesion in the lower pole of the left kidney, mostly protruding beyond the renal contour, measuring ~2.5x3.0x2.6 cm, with progressive enhancement on the contrast scan (Fig. 4). Enhanced chest CT and enhanced brain MRI scans did not reveal any further metastases. Bone scans were negative. The patient was asymptomatic, without abdominal discomfort, hematuria or other urinary system symptoms. It was difficult to distinguish between incidental renal cell carcinoma and renal metastasis based on imaging alone, and the patient refused a biopsy of the renal lesions. Therefore, after multidisciplinary discussion, in a meeting involving urologic oncologists, medical oncologists, radiologists and pathologists, surgical treatment was recommended.

The patient underwent a laparoscopic transperitoneal partial nephrectomy. The postoperative course was uneventful, and the patient was discharged 2 days after surgery. Pathological analysis revealed two pieces of gray-yellow to gray-brown tissue, measuring 5.5x3.0x2 cm, with a gray-yellow cut surface and a small amount of attached fat. Microscopically, the tumor was composed of tightly arranged, small and elongated tubules. Some tumor cells were spindle shaped, with a lightly stained mucinous stroma. The tumor cells forming the tubules were small, cuboidal or oval in shape. No nerves, vascular invasion or intravascular tumor thrombi were detected. Tumor invasion was not detected in the ipsilateral ureter or vascular margins. Immunohistochemistry results revealed the following results: A Ki-67 labeling index of ~20%, paired box protein Pax-8(+), CD117(-), CK7(+), napsin A(-) and TTF-1(-). Based on morphology and immunohistochemistry, the patient was finally diagnosed with high-grade MTSCC (Fig. 5). The patient declined genetic testing due to financial reasons. The tumor was classified as T1N0M0, WHO/International Society of Urological Pathology Grade 3 (23), but without sarcomatoid transformation. According to

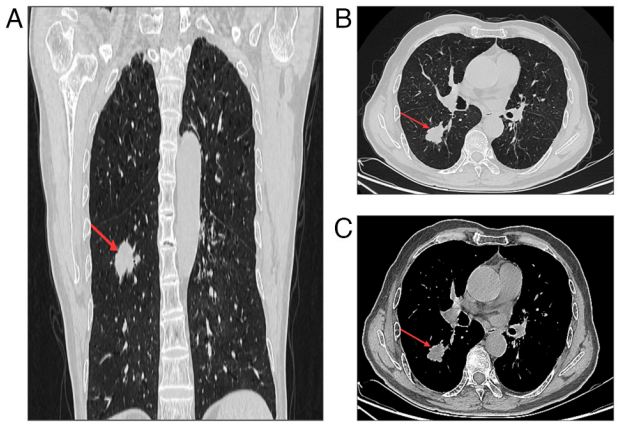

Figure 1. Computed tomography scan of the chest. (A) A lobular soft-tissue mass measuring ~33x26x25 mm was visible in the right lung. In addition, the mass was visible in both (B) lung window and (C) mediastinal window views. Lesions are indicated by red arrows.

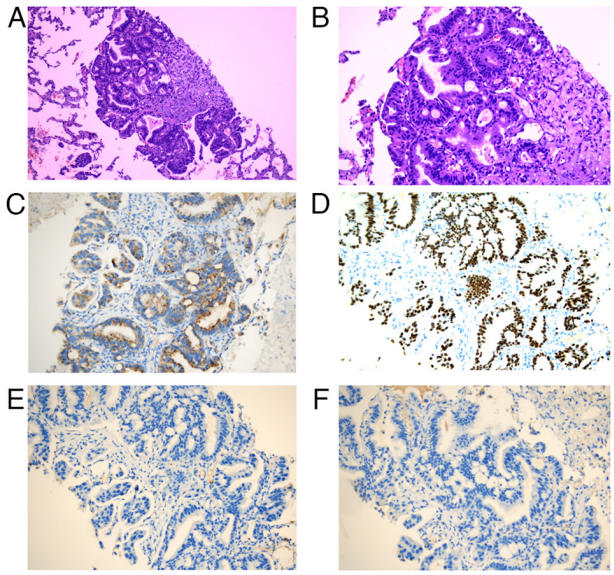

Figure 2. Histological and immunohistochemical findings following lung cancer resection in July 2021. (A) Hematoxylin and eosin staining (original magnification, x100). (B) Hematoxylin and eosin staining (original magnification, x200). Tumor cells were positive for (C) napsin A (magnification, x200) and (D) TTF-1 (magnification, x200). (E) CK5/6 (magnification, x200) and (F) p40 show negative staining (magnification, x200); CK5/6 is a marker for squamous cell carcinoma; NapsinA and TTF-1 are markers for adenocarcinoma. TTF-1, thyroid transcription factor-1; CK, cytokeratin.

the American (UCLA Integrated Staging System) prognostic system (24,25), this patient was classified as low progression risk [TNM stage, T1N0M0; Fuhrman grade (26), 2; Eastern Cooperative Oncology Group performance status (27), 0] (28). Therefore, the postoperative monitoring plan involved clinical examinations (physical examination, tumor markers, creatinine, uric acid and urinalysis) and chest and abdominal CT scans every 6 months for 3 years, then once a year for 2 years, and thereafter once every 5 years. After 3 years of follow-up, the patient remains in good condition, with no local or contralateral recurrence, and no secondary lesions. The clinical timeline for this patient is summarized in Fig. 6. Written informed consent was obtained from the patient for the

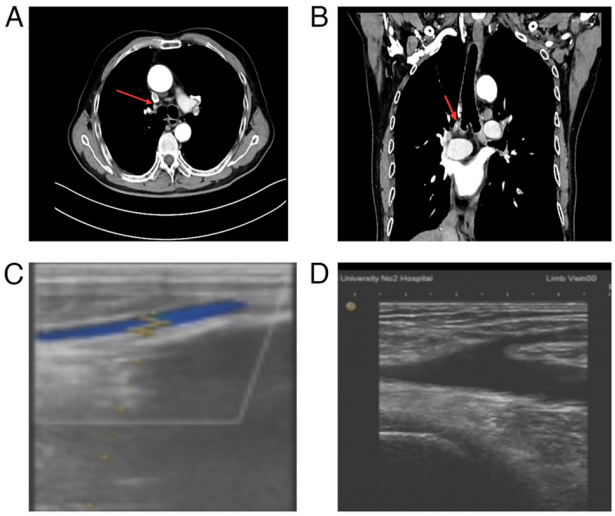

Figure 3. Imaging findings of pulmonary embolism and lower extremity thrombosis. (A) CT scan performed at 3 months post-chemotherapy (axial view) revealing a pulmonary artery embolism in the right upper lobe (indicated by the arrow). (B) CT scan (coronal view) confirming the pulmonary artery embolism in the right upper lobe. (C) Color Doppler ultrasound of the lower extremities revealing a thrombus in the right calf muscle vein. (D) Color Doppler ultrasound (cross-sectional view) further demonstrating the thrombus within the right calf muscle vein.

publication of this case report and any accompanying images. At initial diagnosis, the patient presented with an elevated CEA level, which normalized after surgery. The detailed laboratory monitoring during treatment and follow-up, including tumor marker, uric acid, and creatinine levels, is summarized in Tables SI and SII.

Pathological analysis. All postoperative specimens were fixed in 4% neutral formaldehyde, routinely dehydrated and embedded in paraffin. Continuous sections 4-μm thick were prepared and stained with hematoxylin and eosin (HE). Immunohistochemistry employed the SP method. Primary rat anti-human monoclonal antibodies for CK5/6 (cat. no. ZM-0313; dilution, 1:120), p40 (cat. no. ZM-0472; dilution, 1:60), Napsin A (cat. no. ZM-0473; dilution, 1:100) and TTF-1 (cat. no. ZM-0270; dilution, 1:100) were purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. Immunohistochemical procedures strictly followed kit protocols. PBS served as the primary antibody negative control. TTF-1 and Ki-67 was localized to the nucleus, with positive expression appearing as yellow-brown granular deposits in the nucleus. NapsinA positive staining was located in the cytoplasm, appearing as punctate or granular staining. p40 positive staining was predominantly cytoplasmic, appearing as yellow or brownish-yellow granules. p63 staining was considered positive only when diffusely strongly expressed in the nucleus. Cells were graded by percentage as follows: No positive cells (-); <30% positive cells (+); 30-50% positive cells (++); and >50% positive cells (+++).

Discussion

The patient in the present case was diagnosed with metachronous NSCLC and MTSCC. For cancer survivors, detecting

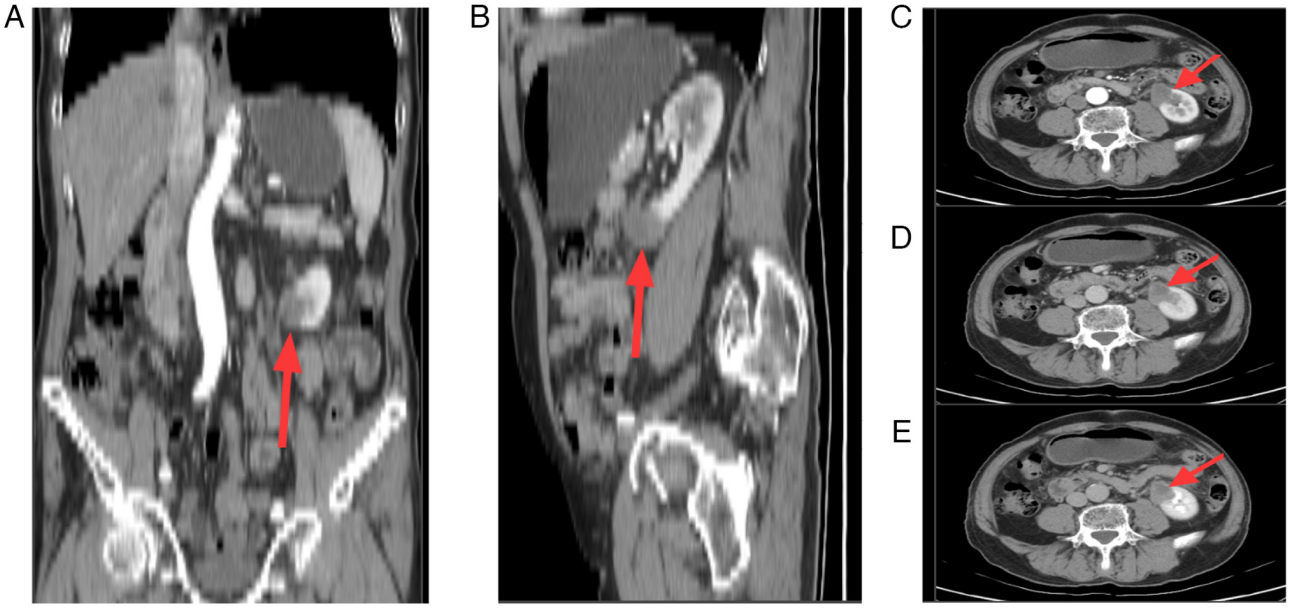

Figure 4. Results of preoperative abdominal contrast-enhanced CT. Abdominal contrast-enhanced CT showed a 2.5x3.0x2.6-cm tumor in the lower pole of the left kidney. (A) Coronal view. (B) Sagittal view (red arrow) revealed a well-encapsulated mass in the left kidney. (C) Contrast-enhanced CT scans showed mild enhancement that was less than that for the cortex in the cortical phase (62 HU). (D) The attenuation of the tumor (80 HU) was slightly increased (red arrow) in the medullary phase. (E) In the delayed phase, the attenuation of the tumor decreased to 75 HU (red arrow). CT, computed tomography.

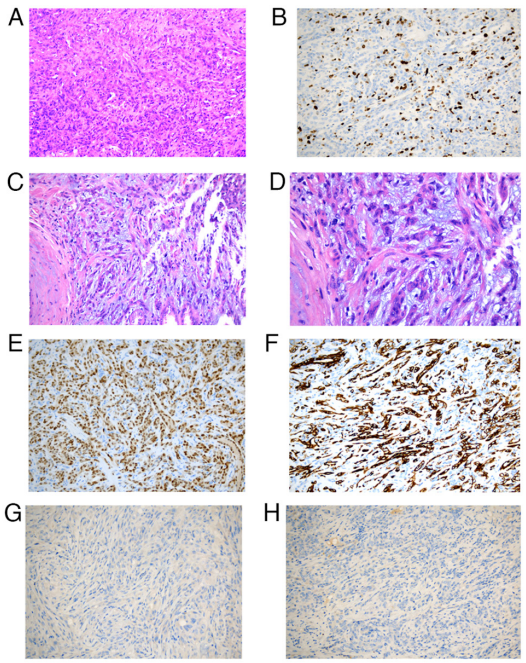

Figure 5. Histological and immunohistochemical findings. (A) The tumor consisted of densely packed, small and elongated tubules. Some tumor cells were spindle shaped. A pale, mucinous-like stroma was visible. Tubule-forming tumor cells were small, cuboidal or oval (hematoxylin-eosin staining; magnification, x200). (B) Positive cytoplasmic staining of Ki-67 (magnification, x200). (C and D) The stroma was myxoid with areas of extracellular mucin (magnification, x200). The tumor cells were positive for (E) paired box protein Pax-8 and (F) cytokeratin 7. Immunohistochemistry for (G) napsin A (magnification, x200) and (H) thyroid transcription factor-1 (magnification, x200) was negative in the left kidney, inconsistent with the primary pulmonary localization.

a new mass necessitates differentiating between metastasis and a second primary malignancy, which directly dictates the

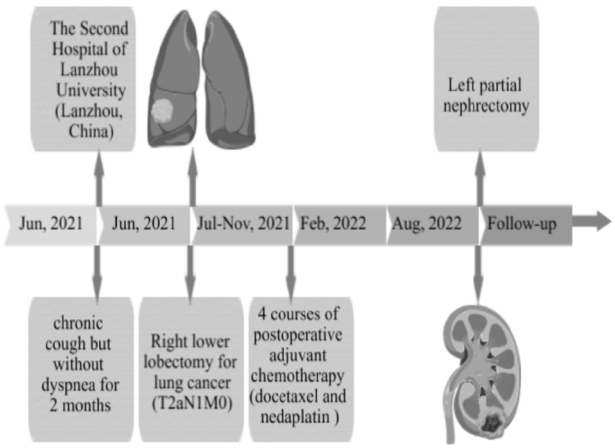

Figure 6. Timeline of treatment interventions. CT, computed tomography.

strategy to be used for clinical management. To the best of our knowledge, no previous cases of these concurrent tumors have been reported in the literature.

NSCLC is the leading cause of cancer-related death and represents ~85% of all lung cancer cases (29). MTSCC constitutes <1% of all renal cell carcinoma (RCC) cases (30). Although initially classified as a low-grade neoplasm, the potential of MTSCC for aggressive behavior has now been recognized, and the term 'indolent renal carcinoma' was removed from the 2016 WHO classification (31-34). Histopathological and immunohistochemical analysis remains the cornerstone for a definitive diagnosis (14). As illustrated in Table I, the systematic application of clinical context, imaging features, distinctive morphology and lineage-specific immunohistochemistry profiles is essential to accurately distinguish MTSCC from renal metastasis and other RCC subtypes.

Table I. Comparison between MTSCC and other relevant differential diagnoses.

Feature	Renal metastasis	Primary renal MTSCC	Primary renal PRCC
Incidence	Relatively uncommon, accounting for 2-12% of renal malignancies. Common primaries include lung, breast and gastric cancers, and melanoma.	Extremely rare, constituting <1% of RCCs. With <100 cases reported in the literature. Female predominance (M:F=1:4).	Relatively common, representing 10-15% of RCCs. The second most common RCC subtype. Slight male predominance.
Key clinical features	i) Often a history of a primary malignancy elsewhere; ii) frequently discovered in the setting of widespread metastatic disease; and iii) may be asymptomatic or present with hematuria/flank pain.	i) Most are incidental findings on imaging; and ii) can present with flank pain or hematuria.	i) Vast majority are incidental findings; and ii) may present with hematuria, flank pain or an abdominal mass.
Imaging characteristics (CT)	Non-specific. Common features include: i) Multiple, bilateral, small (<3 cm) parenchymal masses; ii) mild to moderate, heterogeneous enhancement on contrast; and iii) a wedge-shaped, endophytic growth pattern.	Characteristic 'progressive enhancement': i) Non-contrast: Iso- or hypodense; ii) post-contrast: Mild enhancement in the corticomedullary phase, with persistent, progressive enhancement in the nephrographic/excretory phases ('slow wash-in, slow wash-out'), and less than normal parenchyma.	Also exhibits 'progressive enhancement', often indistinguishable from MTSCC on imaging. i) Non-contrast may be slightly hyperdense (due to hemosiderin); and ii) more prone to cystic change and calcification.
Definitive pathological diagnosis	Morphology identical to the primary tumor. IHC: Pax-8-negative, positive for primary site markers (such as TTF-1 for the lungs).	Pathognomonic: Microscopy shows a triphasic pattern of tightly packed, elongated tubules + spindle cells + pale myxoid stroma, often blending. IHC profile: Pax-8^{+}, CK7^{+}, vimentin^{+}, CAIX^{-}, CD10 (variable; + in the present case). The present case exhibited all of the aforementioned features, with a high Ki-67 (~20%), diagnosing high-grade MTSCC.	Pathognomonic: True papillary structures with fibrovascular cores. Lacks myxoid stroma. IHC profile: Pax-8^{+}, CK7^{+}, CD10 (typically strong/diffuse +) and AMACR^{+}.
Molecular features	Genomic profile matches the primary carcinoma.	Characteristic multiple chromosomal losses (for example, 1, 4, 6, 8, 9, 13, 14, 15 and 22). Absence of gains in chromosomes 7/17.	Characteristic trisomy/multisomy of chromosomes 7 and 17, often with loss of chromosome Y.
Primary treatment	Systemic therapy is the mainstay (chemotherapy, targeted therapy and immunotherapy), based on primary tumor type. Surgical resection or SBRT may be considered for isolated metastases.	Radical/partial nephrectomy is the only curative modality. For high-grade, locally advanced disease (pT2bN1 in the present case), multidisciplinary discussion for adjuvant targeted therapy (such as sunitinib) is warranted post-operatively.	Radical/partial nephrectomy. For advanced/metastatic disease, targeted therapies (such as cabozantinib and sunitinib) or immuno-combinations are used.

Table I. Continued.

Feature	Renal metastasis	Primary renal MTSCC	Primary renal PRCC
Prognosis	Generally poor, dictated by the biology of the primary tumor and metastatic burden.	Bimodal distribution: i) Typical/low-grade MTSCC: indolent, excellent prognosis, near 100% 5-year survival; and ii) high-grade/sarcomatoid MTSCC: Aggressive, significantly worse prognosis, prone to metastasis/recurrence.	Depends on subtype and grade: i) Type I PRCC: Favorable prognosis; and ii) type II or high-grade PRCC: Poorer prognosis, with higher metastatic potential than typical MTSCC.

CT, computed tomography; RCC, renal cell carcinoma; PRCC, papillary RCC; MTSCC, mucinous tubular and spindle cell carcinoma; SBRT, stereotactic body radiotherapy; AMACR, α-methylacyl-CoA racemase. Pax-8, paired box protein Pax-8; TTF-1, thyroid transcription factor 1; IHC, immunohistochemistry; M, male; F, female; CK, cytokeratin; CAIX, carbonic anhydrase 9.

Beyond morphology, elucidating the molecular mechanisms underlying such rare metachronous malignancies holds marked promise. Genomic sequencing could reveal whether these independent primary cancers share common susceptibility factors (for example, germline mutations or signatures of environmental carcinogen exposure) or possess entirely distinct driver profiles. While such analyses were not pursued in the present case due to patient preference and resource constraints, a common challenge in real-world clinical practice, this highlights a critical gap and an important direction for future research. Establishing collaborative frameworks and funding pathways to support the molecular characterization of rare tumor combinations is essential to advance our understanding of their biology and to identify potential therapeutic targets.

The rise in MPMT incidence is likely due to the growing number of cancer survivors, the long-term side effects of chemotherapy and radiotherapy, and the influences from genetic, environmental and endocrine factors (35,36). Tobacco and alcohol use may heighten the risk of multiple independent malignant foci in mucosal epithelial cells (36). Radiotherapy is also implicated in the development of MPMTs (37). In the context of molecular mechanisms, a potential commonality between lung adenocarcinoma and MTSCC may lie in the dysregulation of the Hippo signaling pathway. In lung adenocarcinoma, functional inactivation of the upstream kinases mammalian STE20-like protein kinase 1/2 is associated with tumor progression and can lead to aberrant activation of the downstream oncogenic effectors yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (38). Notably, MTSCC is characterized by a distinct molecular alteration, namely, the frequent occurrence of biallelic loss of core Hippo pathway tumor suppressor genes, such as protein tyrosine phosphatase non-receptor type 14, neurofibromin-2 and salvador homolog 1. This genetic loss similarly results in persistent nuclear accumulation and activation of YAP1 (39,40). Therefore, the inactivation of the Hippo pathway and the consequent dysregulation of its key downstream effectors may serve as a plausible molecular explanation for the co-occurrence of these two metachronous malignancies. This observation also provides a rationale for future exploration of therapeutic strategies targeting this pathway.

The present case highlights key clinical implications. First, an integrated diagnostic approach combining clinical features, imaging and definitive pathology is essential. Second, the case emphasizes the need for structured, long-term, cross-organ surveillance in cancer survivors, particularly those with persistent risk factors. Finally, management should adopt a multidisciplinary team framework, prioritizing curative surgery when possible, with adjuvant therapy guided by specific pathology and the stage of each primary tumor.

In summary, enhancing awareness of multiple primary malignancies is crucial to avoid misdiagnosis. Distinguishing between metastasis and an independent primary tumor directly guides therapeutic strategy and prognosis. Regular follow-up and lifestyle modifications, such as smoking cessation, remain integral to comprehensive survivorship care.

In conclusion, the present study reports a rare case of metachronous primary NSCLC and MTSCC. The case highlights a critical clinical principle in that, for all cancer survivors, a new mass should be investigated as a potential second primary malignancy and not merely presumed as representing metastatic disease. Accurate differentiation relies upon definitive histopathological and immunohistochemical evaluation. Finally, the case emphasizes the necessity of maintaining a high index of diagnostic suspicion and implementing structured and long-term surveillance to optimize outcomes in patients with multiple primary tumors.

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Availability of data and materials

All data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

JXZ conceived the study, acquired, analyzed and interpreted the data, and wrote the manuscript. PFS contributed to the clinical interpretation and differential diagnosis, and critically revised the manuscript. WZ performed pathological evaluations and revised the manuscript as a pathologist. JXZ, PFS, JBP and WZ contributed to clinical investigation and data acquisition (dialysis parameters, laboratory and imaging data), participated in diagnostic discussions, conducted the literature review, revised the Discussion and critically revised the manuscript. JXZ and PFS confirm the authenticity of all raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of the Second Hospital of Lanzhou University (Lanzhou, China; approval no. 2024A-803).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report, including any potentially identifiable images or data.

Competing interests

The authors declare that they have no competing interests.

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