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Case Report

Esophageal squamous cell carcinoma metastases to kidney and renal hilar lymph nodes through epithelial-mesenchymal transition: a case report and literature review

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Abstract: Background: Esophageal cancer (EC) metastasized to the kidney is extremely rare clinically. Here, we present a case of metachronous renal metastasis of esophageal squamous cell carcinoma (ESCC) through epithelial-mesenchymal transition (EMT). Case presentation: A 60-year-old patient, male, complained of left waist pain for 5 days, 11 months after radical esophagectomy. Laboratory tests revealed haematuria. Both CT and PET-CT scan showed retroperitoneal lymph nodes and left renal masses. Subsequently the patient received a left nephrectomy and lymph nodes resection, and squamous cell carcinoma of kidney and renal hilar lymph nodes was diagnosed, combined with morphology, medical history and immunophenotype, it was presumed to be metastasis of ESCC through the EMT pathway. Conclusions: The renal metastasis of squamous cell carcinoma should be considered in patients with history of EC, although this is very rare. Histopathological examination combined with immunochemical detection is helpful in differential diagnosis.

Keywords: Esophageal cancer, metastasis, renal tumor, histopathology, immunohistochemistry, CT, PET/CT

Introduction

Despite of the progress of diagnosis and therapy in recent decades, esophageal cancer (EC) remains one of the leading causes of death due to cancer worldwide [1]. Globally, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) are the two main EC histological subtypes, which accounts for 80% and 20% of EC cases, respectively [2]. EC with regional and distant metastasis has demonstrated 5-year survivals of 25.1% and 4.8%, respectively. Recently, the incidence of distant metastases at newly diagnosed ESCC increases to about 40%-50% in recurrent patients after radical esophagectomy or definitive concurrent radio-chemotherapy [3, 4]. The most common sites of distant metastasis were liver, lung, bone, adrenal glands and sometimes the brain [5]. As reported in a systematic review focused on unexpected metastasis sites in ESCC, only 6.0% (10/164) were found to be renal [6]. We reviewed the published papers in PubMed using keywords "esophageal" and "kidney metastasis" or "metastatic renal tumor", the results displayed that only 20 cases were reported and no molecular mechanisms were reported. Here, we presented a case of metachronous renal metastasis of ESCC and its clinical, imaging, and pathological features were reviewed, at the same time the possible molecular mechanisms were studied. These results may contribute to being able to identify the source of metastatic renal squamous cell carcinoma and plan individualized therapy.

Case presentation

A 60-year-old male patient complained of left waist pain for 5 days after radical esophagec-

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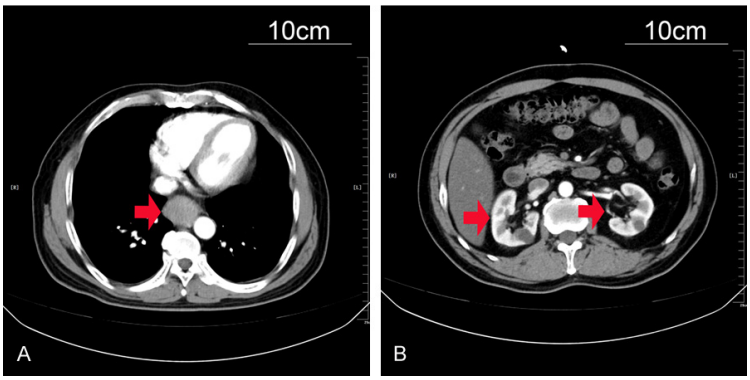

Figure 1. CT scan images of primary esophagus tumor and normal kidney before esophagectomy. Sixty four-slice CT scan image of primary tumor of esophagus (A) and normal kidney (B) before esophagectomy.

tomy 11 months prior and was admitted to the Cardiothoracic Surgery Department of the Joint Logistic Support Force 989 Hospital of Chinese PLA in December 2023. The patient had a history of ESCC with the positive for CK-pan, P40 and P63, negative for CK20, and no mass was detected in double kidneys in December 2022 (**Figures 1**, **2A-C**). He received radical esophagectomy using thoracoscopy in January 2023 and the pathological diagnosis was intermediate differentiated SCC, ulcer type, stage pT3N1 (2/27 metastatic lymph nodes), and the tumor thrombus was observed in vessels (**Figure 2D**, **2E**). The tumor cells of ESCC were strong positive immunochemical staining for P40, P63, CK18, vimentin, β-catenin, weak positive for E-cadherin and negative for CK20 (**Figure 2F-H**). The patient was given adjuvant chemotherapy after surgery. In May 2023, CT scan revealed enlarged retroperitoneal lymph nodes of 9.7×5.4 mm 4 months after esophagectomy. Accordingly, the patient was treated with Camrelizumab and adjuvant chemotherapy. The patient had no other medical history except that his father died of ESCC. Laboratory tests revealed haematuria with increased red blood cells in urine sediment of 137.28 (normal range, 0-5 p/ul). The blood urea nitrogen level, sodium, potassium and calcium in serum was normal. A mass in the left renal of about 42×41 mm and enlarged retroperitoneal lymph nodes of 17.8×18.9 mm was observed by CT (**Figure 3A**, **3B**). A FDG-PET/CT scan with attenuation showed significantly increased uptake of FDG in the left renal lesion with the SUV max of 7.5 and cross section max 46×43 mm, and retroperitoneal lymph node with SUV max of 2.7 (**Figure 3C-I**).

Subsequently the patient received a left nephrectomy and lymph nodes resection. Macroscopically, the renal tumor was measured 5 cm in its largest dimension (**Figure 4A**). A group of enlarged renal hilar lymph nodes were detected. Microscopically, the tumor in kidney and lymph nodes (3/4) was composed of polygonal cells with polymorphic nuclei and some keratinizing cytoplasm, and the tumor cells were arranged in sheets or nests (**Figure 4B**, **4C**), which was identical to that of the previous EC (**Figure 2A**, **2D**). The urothelium was inflamed without evidence of malignancy. The tumor in the left kidney showed positive immunochemical staining for CK-pan, CK-19, CK-5/6, P40 and P63, and negativity for CK7, CK20, Pax8, and CAIX (**Figure 4D-H**). Additionally, the tumor in the left kidney and renal hilar lymph nodes showed positive immunochemical staining for E-cadherin, and negativity for vimentin (**Figure 4I-L**). Presently, the patient is still alive without recurrence and metastasis until March 2024.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

Literature review

Methods of literature review

This systematic review started from a very broad search process to include every possible article. A systematic medical literature search was conducted by the researchers to identify the articles describing renal metastasis of EC between 1987 and February 2024 in the PubMed database. Using the following key words, “esophageal” and “kidney metastasis” or “metastatic renal tumor”, 6258 articles were identified. Only case reports, case series, and editorial letters that described the renal metastasis of EC were included. By reviewing the titles and abstracts of these articles, 16 articles were selected for present literature review.

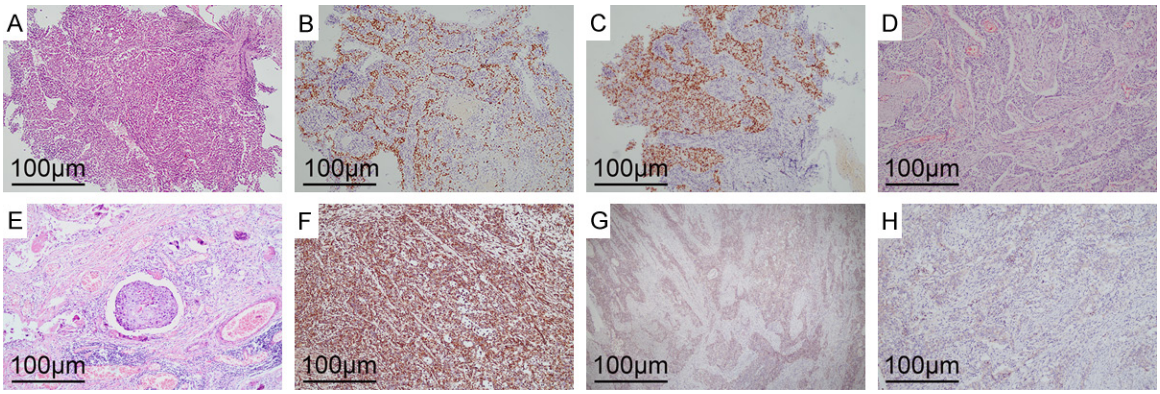

Figure 2. Hematoxylin and eosin (H&E) staining and immunochemical staining of primary in present case. H&E staining of primary tumor (A) and positive immunochemical staining for P40 (B) and P63 (C) in the esophageal biopsy specimen. H&E staining of primary tumor (D), the tumor thrombus in vessels (E), positive immunochemical staining for vimentin (F) and β-cateninin (G), immunochemical staining for downregulated E-cadherin (H) in esophagectomy specimen (100×).

Results of literature review

EC metastasized to the kidney was seldom encountered clinically. The present case and the 20 previously reported cases in the literature are briefly listed in **Table 1** [7-22]. Twenty cases were males and one was female. Five cases also had concomitant lung, brain or lymph nodes metastases among them. Only one was adenocarcinoma, the rest were SCC. Nineteen cases involved in unilateral renal metastasis, one case involved bilateral renal metastasis, and one case was not available. Among the 21 cases, two cases were synchronous metastasis to kidney and 19 were metachronous renal metastasis. Additionally, 19 cases were of East Asia ethnicity, and two were of French. Although cancer incidence and histologic type show a geographic difference, ESCC seems to have more of a tendency toward renal metastasis than EAC [2].

Discussion

Renal metastasis is rare, however, the primary tumor sites of renal metastasis is involved in many organs. The rate of renal metastasis was reported to be 7.2% in a study on 11,328 autopsies [23]. The most common primary tumor sites of renal metastasis were the lung (43.7%); colorectal region (10.6%); ear, nose, and throat (6%); breast (5.3%); soft tissue (5.3%); and thyroid (5.3%) [24]. Besides of EC, the uncommon primary tumor sites were reported in recent years from intrahepatic cholangiocarcinoma, primary hepatocellular carcinoma, cervical carcinoma, ovarian granulosa cell tumor, prostate cancer, osteosarcoma with IVC thrombus [25-30]. These made the diagnosis and differential diagnosis of the primary tumor sites of renal metastasis difficult.

Presently, there was no clinical, imaging, morphological, and histopathological features to distinguish the metastatic SCC or adenocarcinoma from the primary one of the kidney. For the typical clinical manifestations, hematuria, flank pain and mass occurred mainly in advanced stage of renal cancer. Renal metastasis from EC was often asymptomatic and diagnosed by CT scan accidentally. The present case received CT scan 2 months, 4 months, and 6 months after esophagectomy, respectively. CT scan revealed enlarged retroperitoneal lymph nodes after esophagectomy 4 months and 6 months. Unfortunately, CT scan was interrupted months after due to esophagectomy. The patient complained of flank pain 11 months after surgery, and then the urine occult blood was found by laboratory detection and renal mass was found by CT scan. During the time since 6 months to 11 months after esophagectomy, the patient did not undergo any examinations, such as CT scan or urine laboratory tests.

CT scan is recommended to screen the recurrence and metastasis after operation of patients with EC. Although in this method it is difficult to differ the metastatic tumor from the

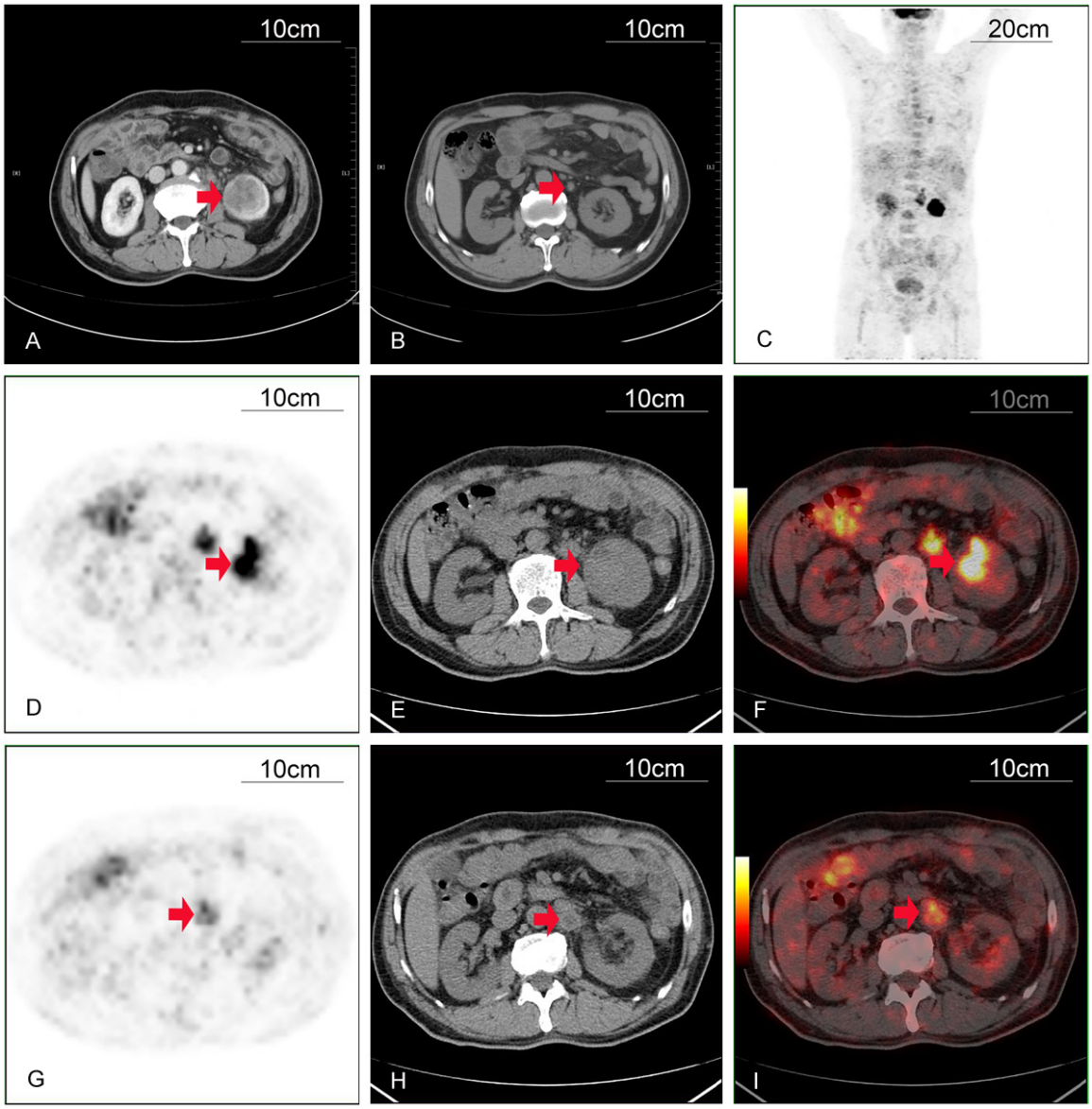

Figure 3. CT and PET-CT scan images of metastatic tumor in the left kidney and retroperitoneal lymph nodes. Sixty four-slice CT scan image of metastatic tumors of left kidney (A) and further enlarged retroperitoneal lymph nodes 11 months after esophagectomy (B). PET-CT scan images of body (C), a left renal metastatic tumor (D-F) and metastatic retroperitoneal lymph nodes (G-I) with significantly increased uptake of ^{18}F-FDG.

primary renal tumor, it can offer important information for the diagnosis of renal metastasis of EC. As showed in present case, CT scan displayed metastatic lesion that appeared as a solitary tumor infiltrating the renal parenchyma and enlarged retroperitoneal lymph nodes.

PET/CT has been reported to be more sensitive to find distant metastasis of ESCC than conventional imaging with CT and endoscopy/endoscopic ultrasonography in the detection of distant metastatic disease [31]. Whole-body PET or PET/CT is recommended for staging of EC in many guidelines. A case of synchronous renal metastasis of ESCC with a small solitary lesion in renal parenchyma was found by PET/CT, which was identified by CT scan almost 7 months later [22]. In this case, significantly increased uptake of FDG in the left renal lesion and retroperitoneal lymph node was verified using PET/CT. So PET or PET/CT scan should be under consideration for metastasis of unusual sites including kidney.

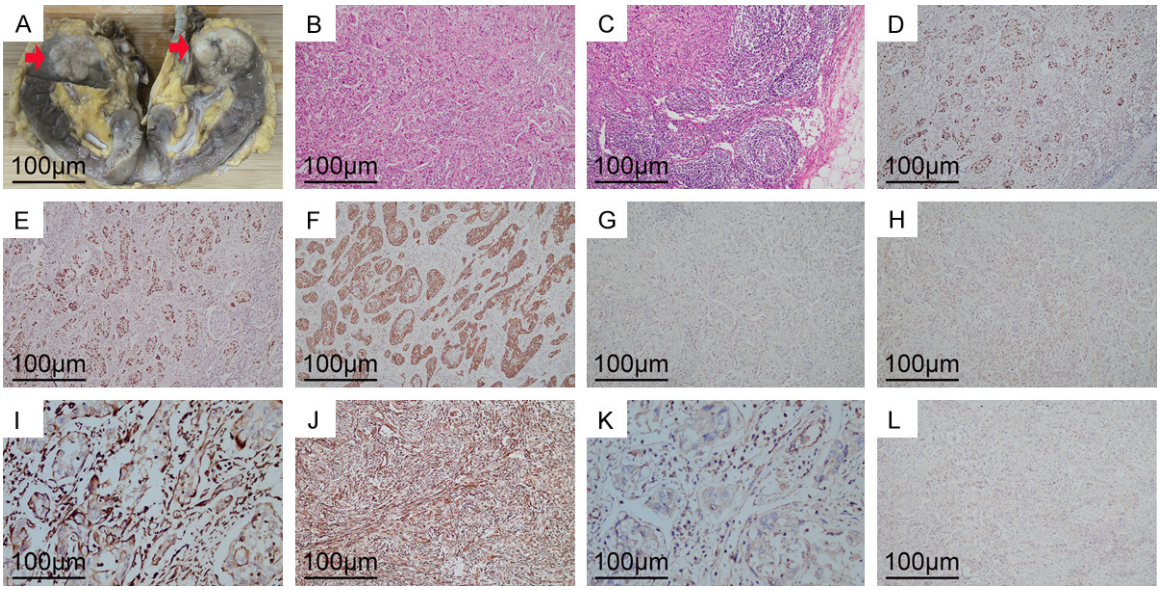

Figure 4. Hematoxylin and eosin (H&E) staining and immunochemical staining of metastatic tumors in present case. Gross photography of the left renal tumor (A). H&E staining of left renal metastatic tumor (B) and renal hilar lymph nodes metastasis (C) under light microscope. Makers of squamous cell carcinoma including P40 (D), P63 (E) and C/K5-6 (F) were positive while markers of renal cancer including PAX8 (G) and CAIX (H) were negative in renal metastatic tumor by immunochemical staining (100×). E-cadherin (epithelial lineage genes) upregulated in the renal cancer (I) and renal hilar lymph cancer (J), while vimentin downregulated in the renal cancer (K) and renal hilar lymph cancer (L) (400×).

Histopathologic examination was commonly used to differentiate between primary and metastatic renal tumors effectively. In recent years, biopsy of renal lesion could make diagnosis before give more aggressive interventions. Distinguishing metastatic SCC from urothelial carcinomas with extensive squamous differentiation is difficult. Additionally, SCC derived from different organs have similar morphological features. In this situation, thorough sampling and careful examination were required to get clues as to the primary site of neoplasms. Sometimes, the complete absence of urothelial precancerous lesions was highly suggestive of a metastatic disease. Usually, the histological type (SCC or adenocarcinoma) can be identified by routine H&E stained slides and immunochemical biomarkers, such as P40, P63, CK5/6, CK20, CK7, and so on. In the present case, the renal tumor was diagnosed as SCC with the aid of CK5/6(+), P63(+) and P40(+), and the CK7(-)/CK20(-) co-negative immunoprofile indicated metastatic SCC [32]. The negative staining of Pax8 and CAIX, which were common biomarkers of renal carcinoma, excluded the diagnosis of primary urothelial cancer [33]. Unfortunately, there were still no specific markers to identify SCC derived from different origins. The history of ESCC and evidence of other metastatic sites were crucial factors to diagnose renal metastasis. In present case, the history of ESCC, tumor thrombus in vessels and the negative evidence of other primary tumors contribute to the diagnosis of renal metastasis of ESCC. Comprehensive morphology, immunophenotyping, imaging findings, the metastatic ESCC in kidney and renal hilar lymph nodes were diagnosed. Maybe genomic the signature could provide more detailed molecular characteristics of cancer cells. Comparing genomic signatures of both primary cancer and metastatic tumor might also be useful to exclude renal primary SCC, as of the present time it has not been reported in the diagnosis of renal metastasis of ESCC.

It was reported that the median survival rate was only 16 months if the hematologic metastasis of the EC occurred [34]. As recommended, treatment strategies for metastasis ESCC was systematic therapy. However, whether nephrectomy is beneficial for patients is controversial because of the rarity of cases. Among the 21 cases of metastatic SCC of the kidney, 15 patients received a nephrectomy, 5 patients received concomitant adjuvant chemotherapy,

Table 1. Reported cases of esophageal cancer with renal metastasis

Case	Age/ Gender	Renal metastasis	Interval between metastasis and primary tumor (months)	Tumor type	Other metastasis	Symptoms	Treatment	Survival time after renal metastasis (months)
Pollack et al. 1987 [7]	62/male	NA	NA	SCC	No	NA	NA	2
Grise et al. 1987 [8]	56/male	Single side	24	SCC	No	Haematuria	Nephrectomy	6
(Two cases)	62/male	Single side	5	SCC	No	Haematuria	Nephrectomy	6
Kitami et al. 1987 [9]	61/male	Left renal	11	SCC	No	Flank pain, fever	Left nephrectomy, chemotherapy	2
Okamoto et al. 1988 [10]	46/female	Right renal	8	SCC	No	Flank pain	Nephrectomy, chemotherapy	6
Nagai et al. 1989 [11]	50/male	Right renal	24	SCC	No	Flank pain, haematuria	Nephrectomy, radiotherapy	4
Shimizu et al. 1990 [12]	62/male	Left renal	5	SCC	No	No	Radiotherapy, chemotherapy, surgery	NA
Miyoshi et al. 1997 [13]	57/male	Right renal	2	SCC	No	Flank pain	Surgery	>3
(Two cases)	57/male	Right renal	12	SCC	No	Flank pain, haematuria	Surgery	2
Matsushita et al. 1998 [14]	74/male	Right renal	13	SCC	No	No	Nephrectomy	3
Cruz Guerra NA et al. 2000 [15]	NA/male	Single side	0	SCC	No	No	Nephrectomy	NA
Mao et al. 2003 [16]	64/male	Single side	36	ADC	Brain	NA	NA	>108
Lim et al. 2004 [17]	64/male	Left renal	24	SCC	No	No	Nephrectomy, chemotherapy	NA
Ku et al. 2005 [18]	65/male	Single side	21	SCC	Lung	No	NA	>6
Sun et al. 2014 [19]	63/male	Right renal	9	SCC	No	Flank pain	Nephrectomy	3
Chang et al. 2016 [20]	53/male	Left renal	31	SCC	No	Flank pain, haematuria	Nephrectomy	2
Zhao et al. 2017 [21]	46/male	Right renal	10	SCC	No	Flank pain	NA	NA
(Two cases)	47/male	Both side	9	SCC	No	No	NA	NA
Jia et al. 2021 [22]	66/male	Right renal	0	SCC	Mediastinal lymph nodes	No	Radiotherapy, chemotherapy, surgery	13
(Two cases)	60/male	Left renal	23	SCC	Lung metastasis	No	Chemotherapy, anti-EGFR	6
Present case	59/male	Left renal	12	SCC	Renal hilar lymph nodes	Haematuria	Nephrectomy	>3

SCC, squamous cell carcinoma; ADC, adenocarcinoma; NA, not available; EGFR, epidermal growth factor receptor.

3 patients received radiotherapy and 1 patient received anti-EGFR therapy. Tumor-free survival time after diagnosis was variable, ranging from 2 months to more than 9 years. Unfortunately, the efficacy of the nephrectomy and adjuvant therapy could not be concluded from the current reported cases because of the limited follow-up time. Recent advances in immunotherapy, such as immune checkpoint blockade therapy, adoptive cellular therapy and vaccines, have revolutionized cancer treatment paradigms [35]. These advances may contribute the therapy of renal metastasis of EC.

Intravasation of tumor cells into vascular or lymphatic channels is involved in the cascade of metastasis. Tumor thrombus in vessels in the primary tumor show great potential for distant metastasis. In present case, the tumor cells may be disseminated to the kidney and renal hilar lymph nodes through the blood because tumor thrombus in vessels in primary ESCC was observed.

One of the tumor metastasis mechanism was Epithelial-Mesenchyma transition (EMT). Once cancer cells are invasive to the tumor stroma, tumor cells have the capacity to disseminate into circulation and colonize distant organs [36]. EMT was a key driver of tumor cell invasion and metastasis during cancer progression, which was marked by down regulation of epithelial lineage genes, such as E-cadherin, and the upregulation of mesenchymal lineage genes, such as vimentin. These phenotypic changes corresponded to the shift in physiology of the cell undergoing EMT, as it gradually looses the ability to form tight junctions with neighboring cells and acquired greater mobility [37]. Mesenchyma-epithelial transition (MET) is the reversion of EMT and is apparent during development, inducing pluripotent stem cell reprogramming, and tumor metastasis, which is marked by up regulation of epithelial lineage genes, such as E-cadherin, and the downregulation of mesenchymal lineage genes, such as vimentin [38]. In the present case, EMT was demonstrated in the cancer in esophagus by the downregulation of E-cadherin and upregulation of vimentin, while MET was demonstrated in the cancer in kidney and renal hilar lymph nodes by the upregulation of E-cadherin and downregulation of vimentin.

Wnt/β-catenin signaling has been broadly implicated in human cancers and experimental cancer models of animals. Aberrant Wnt/β-catenin signaling had been uncovered to be tightly woven with many aspects of cancers, including the onset, progression, malignant transformation, and so on [39]. In the present case, the accumulation of β-catenin in the cancer of esophagus indicated that cancer cells spread to the kidney and renal hilar lymph nodes through EMT involving the activation of the Wnt/β-catenin signaling pathway, which may contribute the targeted therapy of renal metastasis of EC.

Conclusions

In patients with a history of EC, renal tumor should be considered as a metastasis of EC. Imaging detection is helpful to the diagnosis of renal metastasis of EC. Histopathological examination combined with optional immunochemical biomarkers are highly recommended.

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Disclosure of conflict of interest

None.

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