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# Three cases of pleural metastasis of renal clear cell carcinoma diagnosis: cases report

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► *Case Report*

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## ABSTRACT

***Background***: Malignant pleural effusion is common in patients with advanced malignant tumor. The aim of this study is to analyze the characteristics of pleural metastasis of renal clear cell carcinoma, pleural effusion under medical thoracoscopy and the diagnostic value of interventional thoracoscopy-guided biopsy, and to improve the understanding of pleural metastasis of renal clear cell carcinoma. ***Materials and Methods***: 3 cases with pleural metastasis of renal clear cell carcinoma in our hospital were reported. The clinical characteristics and performs were retrospectively analyzed. In addition, a complete resection of tumor nodules was conducted by applying interventional electric knife and cryotechnique with thoracoscopy. ***Results:*** Three cases were all male and presented as dyspnea. By thoracoscopy testing, main lesions showed different size and amount nodules, and pleural thickening and congestion. Tumor tissues had abundant blood supplying and were crisp. Bleeding was easily caused in forcep biopsy, while complete resection of nodules could be achieved by an electric knife, and a larger number of samples were obtained. ***Conclusion:*** To our knowledge, pleural metastasis of renal clear cell carcinoma and formation of pleural effusion are rarely in clinic, most of whom are in male and presented as dyspnea. Medical thoracoscopy can directly displaying thoracic lesions and biopsy of adequate tissue through interventional techniques, which is important in the diagnosis pleural metastasis of renal clear cell carcinoma.

***Keywords:*** *Medical thoracoscopy, Pleural metastasis, Pleural effusion, Renal clear cell carcinoma.*

## INTRODUCTION

Malignant pleural effusion is common in patients with advanced malignant tumor, with pulmonary or pleural metastasis frequently detected. There might have an immune interaction between pleural effusion tumor cells and macrophages. The low intensity of PDL1 expression in immune cells is associated with the poor survival of lung cancer patients with malignant pleural effusion [(1)]. Main symptom is dyspnea, which causes serious impact on patients' quality of life and survival time. Renal cell carcinomas (RCCs), which originate within the renal cortex, are responsible for 80% to 85% of all primary renal neoplasms. Transitional cell carcinomas, which originate in the renal pelvis, comprise approximately 8%. Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, occur infrequently. In children, nephroblastoma or Wilms tumor is common. A medullary carcinoma is a rare form of renal cell carcinoma seen in sickle cell disease. Other less common subtypes are clear cell, papillary, and chromophobe [(2)]. Renal clear cell carcinoma is a low-malignant tumor in renal carcinomas, accounting for 2% of human malignant tumors. c

-Met expression is significantly higher in corresponding metastatic sites compared to paired primary tissues. Given that the treatment landscape for RCC has expanded to include small -molecule inhibition of VEGFR, MET, and AXL pathways [3-5]. The studies are informative in that they suggest that testing for biomarkers of response to c-Met inhibitors should be conducted in metastases. The higher c-Met expression is seen with higher FNG and T-stage, which underscores the key role of the c-MET proto-oncogene in tumor development and aggressiveness [6-8]. Main metastatic sites include the lung, lymph node, bone, brain, liver, adrenal gland, and contralateral kidney. Metastasis to the spleen, septum, gallbladder, stomach, pancreas, tongue, breast and other organs are relatively uncommon [9-10], metastasis to the pleura is even rarely reported. 3 patients with pleural metastasis of renal clear cell carcinoma and pleural effusion in our hospital were analyzed, and literatures were reviewed. Meanwhile, interventional medical thoracoscopy was applied for safe and adequate tissue biopsy, providing clinical reference.

## MATERIALS AND METHODS

Case 1 (male; age: 47) was admitted to our hospital due to dyspnea for 2 weeks with pain in the lower left chest. Chest CT showed left pleural thickening, pleural effusion and bilateral multiple pulmonary nodules (Figure 1-A). Tumor markers of CA199 43.11U/ml (slightly elevated), CYFRA21-1, CEA, CA153, NSE and SCC were normal values. Medical thoracoscopy of local anesthesia showed bloody pleural effusion, pleural congestion and edema, and multiple nodules in the parietal wall, visceral layer and diaphragmatic pleura, partially presenting cauliflower-like lesions (figure 1-B). Mesothelial cells and lymphocytes of pleural effusion were detected, and no heterocysts were found. The (left parietal pleura) morphology combined with immunohistochemistry were used to confirm pleural metastasis of renal clear cell carcinoma. Immunohistochemistry results indicated cancer cells CK(+), CA9(+), CD10(+), Vimentin(+), TFE3 (-), CR(-), MC(-), D2-40(-), HMB-45(-), Desmin(-), CK5/6(-), and Ki-67(+, 30～40%) respectively. Renal CT result might be the middle portion of the left kidney as a malignant tumor and treatment was given.

Case 2 (male; age: 47) was admitted to our hospital due to dyspnea for 4 days accompany by chest pain. Chest CT showed nodules in the right pleura, pleural effusion and bilateral multiple pulmonary nodules (figure 1-C). Two months ago, the patient received radical resection of the left kidney because of renal carcinoma. Medical thoracoscopy of local anesthesia revealed pleural congestion and thickening, multiple nodules of different sizes in the parietal wall, visceral layer and diaphragmatic pleura, abundant blood supply and partial cauliflower-like changes (figure 1-D). Cytological smear of pleural effusion demonstrated amount of mesothelial cells and a few lymphocytes. Morphology and immunohistochemistry conformed to pleural metastasis of renal clear cell carcinoma and treatment was given.

Case 3 (male; age: 54) was admitted to our hospital due to dyspnea for 5 days, and had history of hypertension and diabetes. Chest CT results showed nodules in the right pleura and pleural effusion (Figure 1-E). CYFRA21-1, CEA, NSE and SCC were normal values respectively. Medical thoracoscopy revealed obviously pleural congestion and thickening, erosion in surface, and multiple globular nodules of different sizes in the parietal wall, visceral layer and diaphragmatic pleura, with abundant blood supply and sphacelus covering, presenting cauliflower-like lesions (figure 1-F). Cytological smear of pleural effusion showed a few heterocysts. Pleural biopsy indicated (right parietal pleura) a malignant tumor, which was highly suspected as pleural metastasis of renal clear cell carcinoma combining. Immunohistochemistry displayed cancer cells CK, Vim, CD10, CA9, RCC (+), TTF-1, CK7, P63, P40, NapsinA(-), Ki-67(+, 10-20%), respectively. Renal CT indicated that the left kidney was suspected as a malignant tumor. Systemic chemotherapy treatment was given.

### *Stereotactic radiotherapy (SRT)*

The stereotactic body-frame (marketed by Elekta Oncology Systems) was designed and constructed by Flanigan [11] and used for fixation of patients and for locating targets to be treated with an accelerator (6 MV). Indicators mounted inside the frame are visible on CT images, thus defining the stereotactic system. These indicators can be changed to magnetic resonance (MR) indicators as well. Positions of patients are fixed within the frame by means of a vacuum pillow or a foam cushion.

The cases scales mounted on the outside of the frame according to the CT/MR indicators and we can build isocenter coordinates in the treatment room. The size of the frame allows for use in CT and MR scanners about 55 cm or more. A diaphragmatic pressure device was used to minimize diaphragmatic motions to generally 5 mm.

A clinical target volume (CTV) was defined on CT scans. In most cases it was identical with the gross tumor volume (GTV). Around the CTV a margin of 5-10 mm was added in the transverse and 10 mm in the cranio-caudal directions to obtain the planning target volume.

### *Chemotherapy*

Sunitinib was given orally at 50 mg once daily for 4 weeks, 2 weeks off dosing schedule and provided by Pfizer, the trial sponsor. IFN-2a was used and provided by Pfizer. IFN was administered by subcutaneous injection thrice weekly on nonconsecutive days at 3 MU per dose the first week, 6 MU the second week, and 9MU later. Intrapatient dose reduction orinterruption of either drug was allowed for management of adverse events depending on their type and severity, according to the protocol [12].

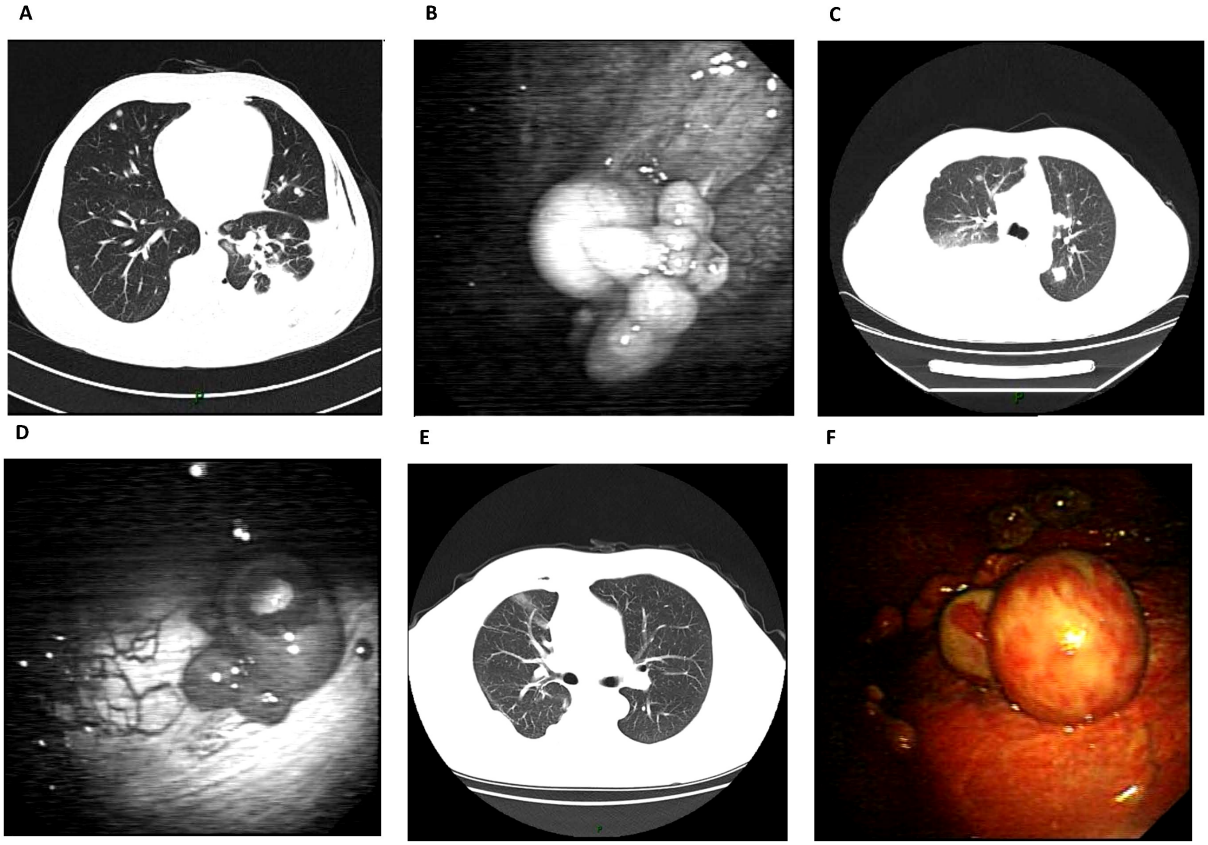


**Figure 1. A)** Chest CT: pleural effusion and bilateral multiple pulmonary nodules. **B)** Medical thoracoscopy: multiple nodules in the parietal wall, presenting cauliflower-like lesions. **C)** Chest CT: pleural effusion and bilateral multiple pulmonary nodules. **D)** Medical thoracoscopy: multiple nodules in the parietal wall, rich in blood supply. **E)** Chest CT: nodules in the right pleura and pleural effusion. **F)** Medical thoracoscopy: multiple nodules in the parietal wall, rich in blood supply.

## DISCUSSION

Renal cell carcinoma (RCC) is a malignant tumor of renal tubular epithelial cells, abbreviated as renal carcinoma. Among them, renal clear cell carcinoma (RCCC) is the most common pathological type, accounting for approximately 75% of renal carcinomas [13]. Early RCCC often no specific clinical manifestations, nearly 1/3 patients had distant metastases when was diagnosed [14], who had missed the best time of surgery. The median survival time was only 13 months [15].

Malignant pleural effusion (MPE) refers to pleural effusion which was caused by primary tumors of pleural tumors or tumors in other parts metastasing to the pleura. Among all malignant tumors, MPE of RCC is rare, accounting for about 1%-2.2% [16]. Basis on the PuMed, CNKI, Google Scholar and other databases searching, a total of 18 cases of pleural metastasis of RCC were found [17-23]. 15 cases were combined with onset from pleural effusion. 5 cases of pleural metastasis of RCCC and pleural effusion confirmed by thoracoscopic biopsy. In this study, a total of 8 cases of pleural metastasis of RCCC and pleural effusion were provided (table 1). Obviously, cases of pleural metastasis of RCC are uncommon. Cases with pathological type confirmed thoracoscopy are rarely. From literatures, pleural metastasis of RCC mostly are males. The 3 cases in this work were also males, consistent with the literature. Main clinical manifestation is dyspnea, which is more obviously after activities. Five cases had a history of RCCC surgery and confirmed postoperative metastasis. 3 cases of CT were accompanied by pulmonary metastasis. RCCC no good tumor markers. Tumor markers always are no abnormalities [19, 20, 22]. It is difficult to definitely diagnose pleural metastasis of RCCC by symptoms, signs and laboratory examinations.

**Table 1.** Characteristics of 8 patients of pleural metastasis of RCCC and pleural effusion.

| Patient | Sex | Age | Side of PE | combined pulmonary nodules | pleural effusion cells | Recurrence | Treatment |
|---|---|---|---|---|---|---|---|
| NO1 Thoroddsen 2002 | M | 47 | Right | No | Negative | No | Support Therapy |
| NO 2 Kamiyoshihara 2007 | M | 68 | Right | No | Negative | Yes | Radiotherapy |
| NO 3 Eckardt 2011 | F | 71 | Right | Yes | Negative | Yes | Oralsunitinib |
| NO 4 Di 2013 | M | 62 | Right | No | Negative | Yes | OralSorafenib |
| NO 5 Yasuda 2016 | M | 61 | Left | No | Negative | Yes | Chemotherapy +Oralsunitinib |
| NO 6 Our study | M | 47 | Left | Yes | Negative | No | Support Therapy |
| NO 7 Our study | M | 47 | Right | Yes | Negative | Yes | Support Therapy |
| NO 8 Our study | M | 54 | Right | No | Atypic cells | No | Chemotherapy |

The confirmation of MPE relies on pathological examination. Pleural effusion cytology is the simplest method to diagnose MPE. The sensitivity of pleural biopsy in diagnosing MPE is lower than that of cytology, showing a diagnostic positive rate of 40%-75% [24]. However, pleural effusion cytology failed to provide pathological results. Imaging of CT and ultrasound-guided percutaneous pleural biopsy can improve the positive rate in diagnosing MPE [25-26].

In our report, 3 patients was accepted medical thoracoscopy of local anesthesia, and intraoperative extraction of pleural effusion for

exfoliative cytology. The flesh-pink globular nodules of different sizes was distributed in the partial pleura or the surface of the diaphragmatic pleura. Pleural thickening, surface congestion and erosion were found. Because of enough blood supplying in tumors, so small vessels were observed. Forcep biopsy showed spongy tumor and obvious bleeding, which can easily cause blood oozing from the wound surface [30]. As for metastatic large pleural nodules, we selected electric snare to remove the entire pleural nodules, which provides more adequate tumor samples comparing with puncture or biopsy forceps. Electric knife burning metastatic nodules may cause the degeneration and necrosis of tumor tissue and vascular occlusion, as well as generate less damage to normal tissue and bleeding. Resected tumors were extracted using freezing method and have good effects. Above patients, exfoliative cytology cannot benefit in pathology and type.

In conclusion, RCCC of pleural effusion is few in clinic. Basis on clinical symptoms and imaging is easily misdiagnosis. Pleural effusion cytology is difficult to definitely diagnose. Thus, early thoracoscopy is suggested for definite diagnosis. For the diagnosis of tumor nodules with abundant pleural blood supplying, local resection of tumor using thoracoscopy combined with electrocautery is suggested.

***Conflicts of interest*: *Declared none.***

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