Case Reports in Oncology

Case Rep Oncol 2020;13:1285–1294

DOI: 10.1159/000509509
Published online: October 16, 2020

Case Report

Spontaneous Regression of Delayed Pulmonary and Mediastinal Metastases from Clear Cell Renal Cell Carcinoma

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Keywords
Oncology · Renal cell cancer · Pulmonary metastasis · Spontaneous regression

Abstract
Renal cell carcinoma (RCC) is often metastatic at diagnosis. Conventional therapies such as chemotherapy, radiotherapy, and hormonal therapy have generally proven ineffective in the treatment of RCC. The abscopal effect, specifically, the ability of localized radiation to trigger systemic antitumor effects, has been reported to lead to regression of non-irradiated distant tumor lesions. Herein, we report 3 patients with non-metastatic clear cell RCC (CCRCC) who underwent a nephrectomy and experienced metachronous pulmonary/mediastinal metastases confirmed as CCRCC. No patients underwent radiation post-nephrectomy or pulmonary metastasectomy. The mean duration was 7.24 weeks from the last negative chest CT prior to the nephrectomy and 96.2 weeks post-nephrectomy. All patients achieved durable complete response by RECIST criteria, with a mean follow-up duration of 115 months. Our case series represents the largest in the literature of patients who underwent a nephrectomy for CCRCC with no pre-existing pulmonary/mediastinal metastatic disease confirmed by chest CT, did not

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undergo radiotherapy, and developed significantly delayed CCRCC pulmonary/mediastinal metastases. We highlight the spontaneous regression of delayed metastatic disease and the role of immune responses in curtailing the growth of pulmonary metastasis in CCRCC.

Introduction

Accounting for more than 100,000 deaths annually worldwide, renal cell carcinoma (RCC) represents 2% of all cancers [1, 2]. Approximately 25–30% of patients with RCC exhibit metastatic disease at the time of diagnosis, and 30–50% of patients subsequently develop pulmonary metastases [1–3]. The lung is the most common site for RCC metastasis, followed by mediastinum, bone, liver, skin, and brain [1]. Conventional therapies such as chemotherapy, radiotherapy, and hormonal therapy have generally proven ineffective in the treatment of RCC [1, 4]. While VEGF tyrosine kinase inhibitors such as sorafenib and sunitinib have been shown to achieve complete remission in a very small percentage of patients, disease progression often ensues [3]. Pulmonary metastasectomy in the appropriate patient population is one of the options for treating pulmonary metastases from RCC. A 5-year survival rate between 21 and 60% compared to 11% for non-operated patients has been reported [2–4].

The abscopal effect, specifically, the ability of localized radiation to trigger systemic antitumor effects, has been reported to lead to regression of non-irradiated distant tumor lesions [5, 6]. Additionally, pre-existing metastases have been shown to benefit from the nephrectomy effect which is associated with the induction of regression following nephrectomy [7, 8]. Subsequent pulmonary metastasis from RCC after nephrectomy with spontaneous regression has rarely been reported [8].

Herein, we describe 3 patients who underwent nephrectomy for clear cell RCC (CCRCC) and subsequently developed pulmonary/mediastinal metastases with confirmed CCRCC which significantly decreased in size or resolved with no surgical or other types of treatment. The mechanisms associated with the abscopal effect and spontaneous regression of pulmonary metastasis due to RCC are discussed.

Methods

Under an Institutional Review Board (IRB)-approved protocol, we reviewed the medical records and imaging studies of 3 consecutive individuals who were diagnosed with non-metastatic CCRCC, underwent a nephrectomy, and subsequently experienced metachronous pulmonary and/or mediastinal metastases confirmed as CCRCC by biopsy. None of the patients was treated with radiation post-nephrectomy, and a pulmonary metastasectomy was not performed following the confirmation of metastatic pulmonary/mediastinal CCRCC in any of the cases.

Results

Demographics

All 3 patients were male with a median body mass index of 37.4 kg/m^2 (34.06–43.79 kg/m^2) (Table 1). Two men had experienced chronic kidney disease, and hypertension was noted in all 3. The patient with sarcomatoid CCRCC (case #1) had a strong family history of gastrointestinal malignancies. He underwent genetic testing which detected no known cancer-causing mutations. The other 2 patients did not undergo genetic evaluations.

Diagnosis of CCRCC and Nephrectomy

Two men underwent a left nephrectomy, while the third had a right nephrectomy (Table 1). The mean age at nephrectomy was 54.7 years (41–68 years). The primary tumor grade was 3 in two cases and 4 in the case with sarcomatoid features in approximately 45% of the tumor. The primary tumor stage was T3 in all 3 patients, and regional lymph node invasion was noted in one case. Synchronous metastases were not observed by a chest CT in any of the patients at the time of nephrectomy. The mean duration was 7.24 weeks (2.0–17.29 weeks) from the last negative chest CT prior to the nephrectomy. CCRCC was histologically confirmed as the primary tumor in all 3 cases.

Pulmonary/Mediastinal Metastases

The mean duration was 96.2 weeks (6.14–176.4 weeks) between the initial nephrectomy and the development of pulmonary/mediastinal metastasis (Table 1). One patient underwent a CT-guided fine needle (20-gauge) biopsy of two 8.0-mm noncalcified nodules in the right lower lobe of the lung (case #1; Fig. 1A–D), while one patient had an endobronchial ultrasound fine needle aspiration (EBUS FNA) of a subcarinal lymph node (case #2; Fig. 2A, B) and one had an EBUS FNA of a hilar lymph node (case #3; Fig. 3A, B). CCRCC was biopsy-proven in all 3 cases. Case #2 also had evidence of a pulmonary nodule in the upper right lung, although this mass was not biopsied (Fig. 2C). It resolved following the EBUS FNA of the subcarinal lymph node (Fig. 2D). The patients received no treatment for the pulmonary/mediastinal metastasis. Case #1 was treated with pazopanib 800 mg per day for 4 days which was subsequently discontinued due to thrombocytopenia and myalgia.

Follow-Up Duration

The mean follow-up duration was 115 months (17–67 months) following biopsy confirmation of the CCRCC pulmonary/mediastinal metastases. All 3 patients underwent serial chest, abdominal, and pelvic CTs. The biopsy-proven pulmonary metastasis in case #1 significantly decreased in size and eventually resolved. The subcarinal and hilar lymph nodes in the other two cases shrunk to non-pathologic lymph node size. Case #1 underwent a left partial nephrectomy for a second primary CCRCC 227 weeks following the biopsy for his pulmonary nodules. This tumor (grade 2, pT1aNx) measured 1.5 cm in greatest dimension. No sarcomatoid or rhabdoid features were identified, and there was an absence of tumor necrosis or lymphovascular invasion.

Discussion

Several processes have been described that may lead to the regression of pulmonary metastases in RCC, including nephrectomy with or without subsequent radiotherapy as well as spontaneous regression [5, 8–11]. Local radiotherapy has a high degree of spatial precision to achieve locoregional tumor control; however, radiotherapy also has the ability to induce a systemic antitumor response leading to regression and rejection of non-irradiated distant tumor nodules [5]. This abscopal effect is based on the theory that radiotherapy is an immune modulator in the tumor microenvironment by inducing cell apoptosis and releasing immunogenic factors through immunogenic cell death (ICD) [6, 10, 12]. ICD leads to an anti-tumor immune response through the release of tumor antigens by irradiated tumor cells [10]. Localized radiation spurs a burst release of cytokines and chemokines that promotes an inflammatory tumor environment [10, 12]. Antigen-presenting cells and T cells are more conducive to recognize and eradicate the primary tumor and metastases at distant sites. Thus, local radiation may induce systemic anti-tumor immune responses with out-of-field lesion regression [5].

Spontaneous regression refers to the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate [13]. In 1928, Bumpus [14] initially described regression of pulmonary metastasis following left nephrectomy for hypernephroma. The frequency of spontaneous regression of RCC ranges between 0.5 and 7.0% [15]. Spontaneous regression is not deemed a cure as later recurrence has been reported [15]. In Janiszewska and colleagues' 40-year review of 59 cases of spontaneous regression of RCC, the cases were categorized into 3 groups: (1) regression of RCC metastasis (n = 48; 30 in the lungs); (2) delayed metastases (n = 5; 4 in the lungs); and (3) regression of the primary tumor (n = 4) [8]. The majority of patients in this review experienced regression of their metastases spontaneously after nephrectomy or embolization of the primary tumor. It has been suggested that resection of the primary tumor (the "nephrectomy effect") may result in the removal of prometastatic or growth factors secreted by the tumor, promotion of apoptosis, and greater tumor antigen exposure leading to a heightened anti-tumoral response by the host immune system [8, 9, 15].

In the category of delayed metastases, all cases were preceded by a nephrectomy performed between 9 and 300 months earlier [8]. Most of these lesions were diagnosed accidentally during postoperative follow-up. The 3 patients described in our case series fulfilled the criteria of this category. Our patients did not have evidence of pulmonary/mediastinal metastasis prior to the nephrectomy as confirmed by a negative chest CT performed a mean duration of 7.24 weeks (2.0–17.29 weeks) earlier. They subsequently developed pulmonary/mediastinal metastasis with a mean duration of 96.2 weeks (6.14–176.4 weeks) post-nephrectomy.

Several mechanisms have been suggested as playing a role in the spontaneous regression of metastatic lesions from RCC, specifically, trauma (fever, infection, surgery, biopsy), hormonal alterations, and changes in blood supply such as inhibition of angiogenesis by cytokines [8, 9, 13]. We propose that the mechanism most likely involved in our case series was initiated by the biopsy that all 3 patients underwent, and their metastases were delayed by several weeks to months post-nephrectomy. We hypothesize that the biopsy led to a tumor antigen release that was exposed to the antigen-presenting cells, activating an immune response

cascade. The immune response is further supported by the radiographic durable complete response of the CCRCC metastasis in the lung and mediastinum and not due to the slow-growing nature of this type of tumor. The CT-guided fine needle (20-gauge) biopsy in case #1 and the EBUS in the other 2 cases were of insufficient size to remove the entirety of the pulmonary/mediastinal metastatic lesions. Additionally, the pazopanib in case #1 likely did not contribute to the spontaneous regression of the metastases as it was discontinued after 4 days due to thrombocytopenia and myalgia.

Conclusion

Our case series represents the largest in the literature of patients who underwent a nephrectomy for CCRCC with no pre-existing pulmonary/mediastinal metastatic disease confirmed by a chest CT, did not undergo radiotherapy, and developed significantly delayed CCRCC pulmonary/mediastinal metastases. Spontaneous regression of delayed metastatic disease is exceedingly rare, especially when there is an absence of synchronous pulmonary/mediastinal metastases. While myriad mechanisms have been proposed to explain the phenomenon of spontaneous regression of metastatic lesions, further investigation is warranted to elucidate the pivotal role of the host's immune response.

Acknowledgment

We acknowledge Norton Healthcare for their continued support.

Statement of Ethics

The Chair/Vice-Chair of the Institutional Review Board at the University of Louisville determined that this study was exempt according to 45 CFR 46.101(b) under Category 4 (IRB number 19.1288). The subjects in this study have given their written informed consent to publish their case including publication of images.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

None.

Author Contributions

L.B.E.S. and A.R.K. substantially contributed to the conception, design, acquisition, analysis, and interpretation of data. L.B.E.S. drafted the manuscript. L.B.E.S. and A.R.K. critically revised the manuscript for important intellectual content and gave final approval.

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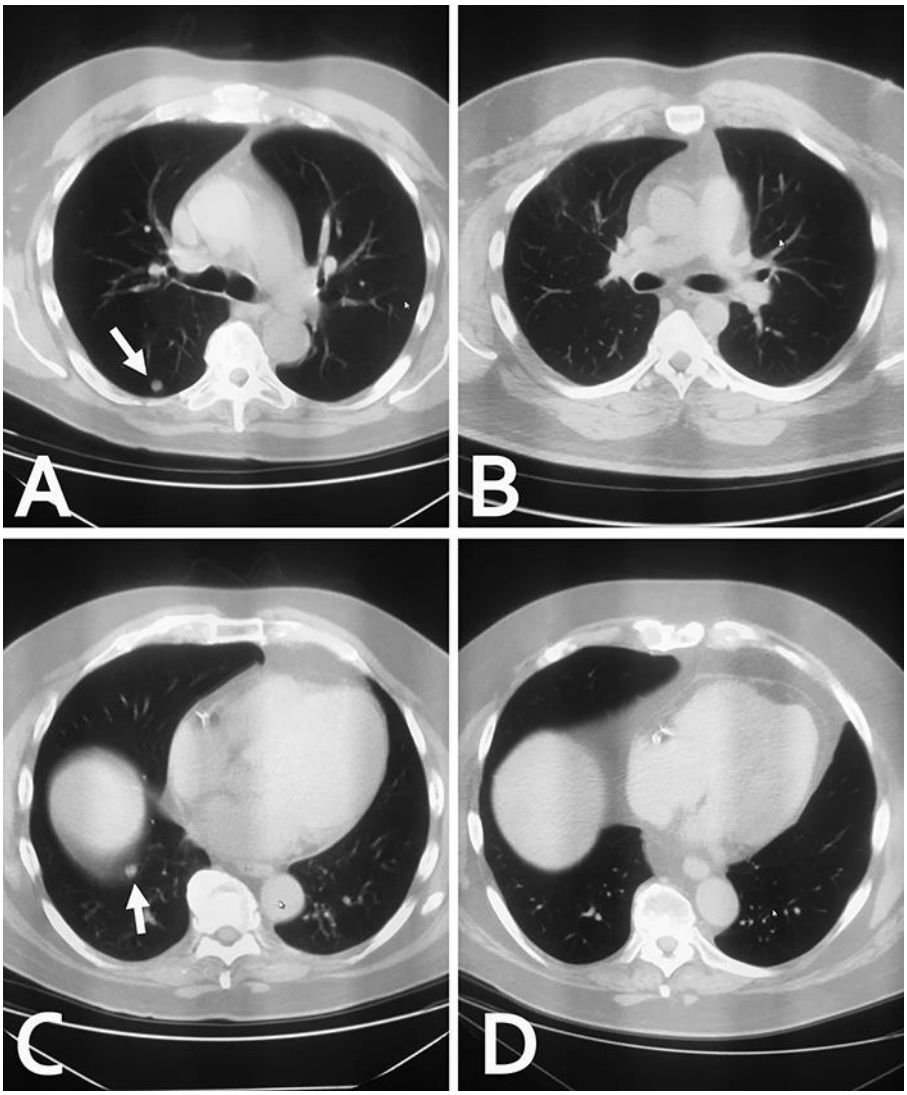

Fig. 1. Chest CT scans demonstrated two noncalcified 8.0-mm pulmonary nodules in the right lower lobe of the lung prior to the CT-guided fine needle biopsy (**A**, **C**) (arrows) and resolution of the pulmonary nodules 13 weeks following the biopsy (**B**, **D**).

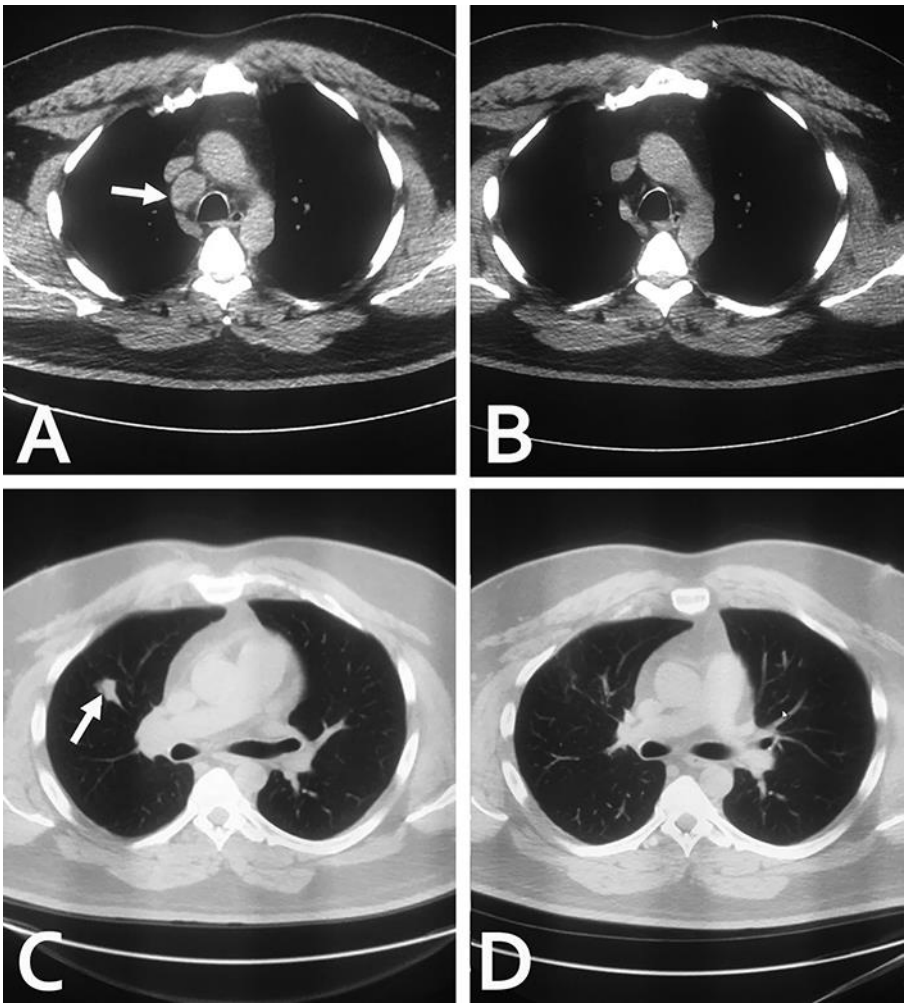

Fig. 2. Chest CT scans revealed a subcarinal lymph node prior the endobronchial ultrasound fine needle aspiration (EBUS FNA) (**A**) (arrow), resolution of the subcarinal lymph node 3 weeks following the EBUS FNA (**B**), pulmonary nodule in the upper right lung prior to the EBUS FNA of the subcarinal lymph node (**C**) (arrow), and resolution of the pulmonary nodule 3 weeks following the EBUS FNA (**D**).

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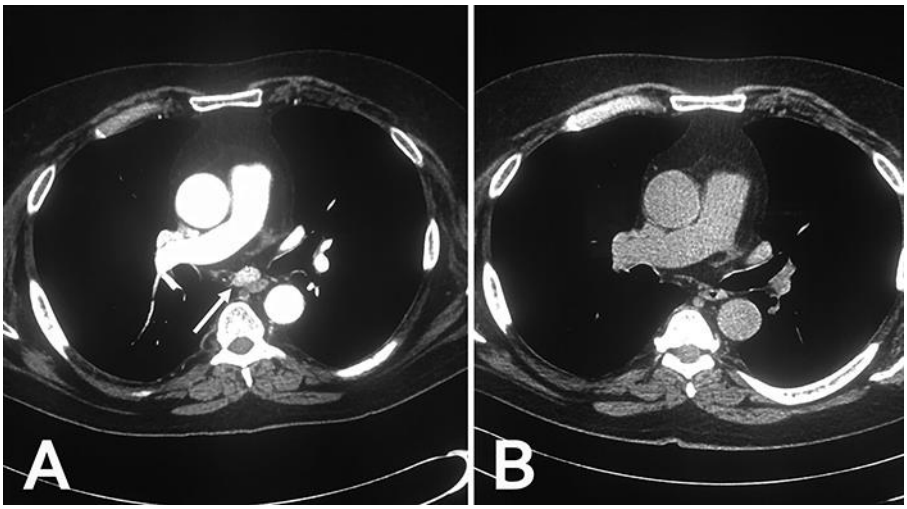

Fig. 3. Chest CT scans showed a hilar lymph node prior to the EBUS FNA (**A**) (arrow) and resolution of the hilar lymph node 5 weeks after the EBUS FNA (**B**).

Table 1. Pulmonary and mediastinal metastases with confirmed clear cell renal cell carcinoma

Metric	Case #1	Case #2	Case #3
Age at nephrectomy, gender	68 years, male	55 years, male	41 years, male
Initial operation	Right nephrectomy	Left nephrectomy	Left nephrectomy
Primary tumor grading	Grade 4 with extensive sarcomatoid differentiation	Grade 3	Grade 3
Primary tumor stage	pT3aNxMx	pT3aN1	pT3aNx
Initial tumor size	13.7×8.5×8.4 cm	5.7×5.5×4.5 cm	8.5×7.0×7.0 cm
Primary tumor nodal status	No regional lymph node invasion	Presence of regional lymph node invasion	No regional lymph node invasion
Synchronous metastases	No	No	No
Primary tumor and pulmonary/mediastinal histology	CCRCC with sarcomatoid features	CCRCC	CCRCC
Co-morbidities	Stage III chronic kidney disease; Htn; obesity; obstructive sleep apnea	Chronic kidney disease, Htn	Htn, diabetes mellitus, sleep apnea
Body mass index	34.27 kg/m^2	34.06 kg/m^2	43.79 kg/m^2
Interval between last negative chest CT and nephrectomy	2.0 weeks	2.43 weeks	17.29 weeks
Interval between nephrectomy and pulmonary/mediastinal metastasis	6.14 weeks	176.43 weeks	106.14 weeks
Age at pulmonary/mediastinal biopsy	68 years	58 years	43 years
Pulmonary/mediastinal procedure	Fine-needle biopsy of 28.0 mm noncalcified nodules in right lower lobe of lung	EBUS of subcarinal lymph node	EBUS of hilar lymph node
Treatment for pulmonary/mediastinal metastases	Pazopanib 800 mg QD for 4 days	None	None
Follow-up duration after biopsy confirmation of CCRCC pulmonary/mediastinal metastases	67 months	31 months	17 months

CCRCC, clear cell renal cell carcinoma; Htn, hypertension; EBUS, endobronchial ultrasound.