Late Pulmonary Metastasis of Renal Cell Carcinoma Resected 25 Years after Nephrectomy

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A 50-year-old male underwent a left nephrectomy for clear cell type renal cell carcinoma (RCC) in February 1978. A right pulmonary metastasis was resected in February 1994. At that time, chest computed tomography revealed the presence of three small nodules in the left lung, but these were followed up as inflammatory lesions. In January 2002, a right pleural metastasis, which showed rapid growth, was detected and it was resected in June of the same year. A gradual growth was observed in the left lung nodules, and the patient underwent wedge resection of the left lung in March 2003, 25 years after nephrectomy. These nodules were diagnosed as metastatic RCC. Currently, the patient is doing well with no signs of recurrence, 8 months after the third metastasectomy.

Key words: renal cell carcinoma – late pulmonary metastasis – repeated metastasectomy – long disease-free interval

INTRODUCTION

Although pulmonary metastases of renal cell carcinoma (RCC) constitute the majority of cancer recurrences following nephrectomy, a disease-free interval of more than 20 years has rarely been reported. We previously reported an RCC patient with a metastatic pulmonary lesion resected 16 years after nephrectomy (1). During the postoperative follow-up, this patient underwent pleural metastasis extirpation in June 2002 and wedge resection of the left lung for pulmonary metastases in March 2003. To the best of our knowledge, the time interval between nephrectomy and metastasectomy is the longest ever reported in English literature from Japan. Therefore, this case is considered worthy of report.

CASE REPORT

A 50-year-old male underwent left nephrectomy for RCC at a university hospital on February 2, 1978. The disease was histopathologically diagnosed as RCC, clear cell type, grade 1, and stage I. In August 1989, an abnormal shadow was detected in the left lung, but it disappeared shortly. This shadow was diagnosed as pleuritis. In September 1993, an abnormal X-ray shadow was detected in an annual health check-up, and the patient was referred to our institution. Computed tomography (CT) revealed a small nodule in the right lung. Video-assisted thoracoscopic wedge resection of the right lung was performed in February 1994, 16 years after nephrectomy. Pathological examination revealed that the tumor was metastatic clear cell type RCC (1).

Chest CT performed before the resection also revealed the presence of small nodules in the left inferior lingular segment and posterior basal segment (Fig. 1a). These were diagnosed as inflammatory nodules following pleuritis, and we decided to use CT to follow them up. CT scans were performed annually, and a pleural tumor adjacent to the right superior and inferior segment was detected in January 2002 (Fig. 2a). Since this tumor showed rapid growth on CT in May 2002 (Fig. 2b), the patient underwent a video-assisted thoracoscopic extirpation of the parietal pleural tumor on June 18, 2002. Histopathological examination demonstrated an RCC metastasis.

CT performed in February 2003 revealed evident growth of the left lung nodules (Fig. 1b). No evidence of other recurrences was detected. On the basis of the diagnosis of RCC metastasized to the left lung, we planned a third resection. The patient presented no symptoms at the time of the third admission in March 2003. Physical examination revealed surgical scars on the abdomen and right-sided chest wall.
Video-assisted thoracoscopic wedge resection of the left lung was performed on March 19, 2003, 25 years after nephrectomy. Three nodules were present in the left inferior lingular and posterior basal segment. These nodules were resected along with the surrounding normal pulmonary parenchyma using stapling devices. No other lesions were thoracoscopically evident.

In macroscopic findings, the resected lung specimen revealed yellowish protruding tumors, visible immediately beneath the pleural surface. Microscopically, the lesion consisted of tumor cells growing in an alveolar pattern, separated by stroma, characteristically endowed with prominent sinusoid-like vessels. The tumor cells had abundant clear cytoplasm and uniform small ovoid hyperchromatic nuclei (Fig. 3a). These histological features are similar to those of the previously resected metastatic lesions (Fig. 3b). The tumor was diagnosed to be compatible with metastatic clear cell type RCC.

The postoperative course was uneventful. The patient was discharged on the 7th postoperative day. Currently, the patient is doing well, with no signs of recurrence, 8 months after the third metastasectomy.

**DISCUSSION**

RCC frequently metastasizes to the lung. The prognosis of unresected metastatic RCC is poor. The 5-year survival rate of patients with metastatic RCC without surgical resection was only 9% (2). Chemotherapy, radiation therapy or immunotherapy has not proven effective for metastatic RCC. Surgical resection for pulmonary metastasis of RCC is a safe procedure (3–7). Complete surgical resection can result in long-term survival (5).

Piltz et al. (5) reported that the recurrence of resectable pulmonary metastases did not impair survival. This favors repeated resection. Pfannschmidt et al. (3) showed that the 5-year survival of patients undergoing repeated resection of pulmonary metastases did not differ from those with resection of a single metastatic lesion. Cerfolio et al. (4) stated that the 5-year survival rate of patients with repeated thoracotomy was similar.
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to that observed for patients with a single thoracotomy. Fourquier et al. (7) reported the same result. These reports suggest that repeat metastasectomies are warranted. In this case, the repeated metastasectomies were safe and uneventful, and the patient is doing well, with no signs of further recurrence.

Poor prognosis following incomplete resection of RCC pulmonary metastasis has been reported. Pfannschmidt et al. (3) showed a 5-year survival rate of 22.1% in patients with incomplete resection as compared to 41.5% in patients with complete resection. Fourquier et al. (7) reported that one among five patients with incomplete resection survived for more than 3 years. However, Jett et al. reported that no difference in survival was detected in patients undergoing complete resection versus incomplete resection or biopsy only (8). Due to these contradictory reports, the role of resection of pulmonary RCC metastases remains unclear.

Pulmonary metastases of RCC with a long interval after nephrectomy have occasionally been reported. To our knowledge, there have been five cases with an interval of 20 years or more (Table 1). Froehner et al. (9) reported a case 20 years after nephrectomy. Jett et al. (8) reviewed their patients, and the maximum interval between nephrectomy and pulmonary resection was 20.5 years. The patient prognosis was not described. Donaldson et al. (10) reported a patient with two pulmonary metastases 24 years after nephrectomy. They performed a left lower lobectomy and right pulmonary wedge resection. A skin metastasis developed the next year, and the

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**Figure 2.** (a) Computed tomography, performed in January 2002, revealing a pleural tumor adjacent to the right superior and inferior segment. (b) Computed tomography, performed in May 2002, revealing evident growth of this tumor.

**Figure 3.** (a) The features of the tumor cells are similar to the previously resected pulmonary metastasis of renal cell carcinoma (Hematoxylin-eosin). (b) Resected lung tumor diagnosed as compatible with metastatic renal cell carcinoma to the lung (Hematoxylin-eosin) (1).
patient died of RCC 2 years after the lung resection. Bradham et al. (11) described a patient with pulmonary metastases 25 years after nephrectomy. Since the tumor had spread, only a part of it was removed for pathological confirmation. The patient died of RCC one year later. In a Japanese report having an English abstract, a 28-year interval was described. The patient was doing well without signs of further recurrence 4 years after resection of the metastatic lesion (12). Friedel et al. (2) reported that patients with a disease-free interval (DFI) of 48 months or more achieved a 5-year survival of 46% as compared to 26% for those with a DFI of less than 48 months. Pfannschmidt et al. (3) concluded that a long DFI was a favorable prognostic factor in cases of pulmonary RCC metastasis. The 5-year survival rate in patients with a DFI of more than 23 months was 47% as compared to 24.7% in patients with a DFI of 23 months or less. Cerfolio et al. (4) reported that patients with DFI more than 3.4 years had better survival rates. However, the prognostic information in patients with a DFI of 20 years or more (Table 1) raises a question regarding the role of the resection of RCC metastatic lesions. Two of the four cases with prognosis and description died of RCC following a relatively short course after resection of the metastasis. The other two were free of disease but for a relatively short follow-up period. In the present case, although, the left pulmonary metastases remained dormant for 10 years, the right pleural metastasis demonstrated a rapid growth. Longer DFI does not always imply slow tumor growth or absence of other metastases.

McNichols et al. reported that late RCC metastases are often combined with rapid disease progression (13). Late relapses after nephrectomy and prolonged stabilization of disease in the absence of systemic treatment and rare spontaneous regressions may suggest that host immune mechanisms are important in regulating tumor growth (14). However, these mechanisms have not yet been fully explored.

In conclusion, the literature data and lack of efficient therapeutic alternatives has lead to aggressive surgical resection of pulmonary RCC metastases being the treatment of choice. However, the true role of resection in management of pulmonary metastatic RCC, especially in patients with a very long DFI, is still unclear.

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Table 1. Time interval of 20 years or more between nephrectomy and resection of pulmonary metastases

| Authors           | Interval (years) | Prognosis                  |
|-------------------|------------------|----------------------------|
| Froehner M et al. (9) | 20              | Patient without RCC for 18 months |
| Jett JR et al. (8)   | 20.5             | Not described               |
| Donaldson JC et al. (10) | 24            | Patient died with RCC 2 years later |
| Bradham RR et al. (11) | 25             | Patient died with RCC 1 year later |
| Yoshikawa K et al. (12) | 28             | Patient without RCC for 4 years |