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Case report

A case of renal cell carcinoma with late recurrence in the bilateral hilar lymph nodes twenty years after surgery

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ABSTRACT

Renal cell carcinoma (RCC) is a common malignancy with a high recurrence rate. However, brain and bilateral hilar lymph node (BHL) relapse is rare. A 65-year-old man with a chief complaint of hemoptysis visited the primary care clinic. Computed tomography revealed BHL enlargement. Histopathological examination of biopsy specimens from the left lingular bronchus revealed RCC. This finding was similar to that of a left nephrectomy specimen of RCC observed 20 years ago. If patients have a medical history of RCC, physicians should consider the possibility of RCC recurrence, regardless of the number of years relapsed postoperatively.

1. Introduction

Renal cell carcinoma (RCC) is a common malignancy and represents 2–3% of all adult cancers [1]. Postsurgical recurrence occurs in 20–30% of patients with localized RCC [2]. Cases of relapse 10 years after initial nephrectomy have been observed in 4.7–11% of patients with RCC [3,4]. Patients with RCC commonly experience delayed distant metastasis in the lungs, bone, and liver 10 years after nephrectomy [5]. Brain and bilateral hilar lymph nodes (BHL) are rare relapse sites of RCC. Herein, we report a case of RCC with an extremely delayed relapse in both the brain and BHL 20 years after radical nephrectomy. A medical history of RCC warrants close attention from the physician to assess the recurrence of RCC.

2. Case report

A 65-year-old man with a chief complaint of hemoptysis visited a primary care clinic. Computed tomography (CT) was performed, which revealed enlargement of the BHL. The patient was referred to our hospital in November 20XX. He had been receiving hemodialysis for renal failure due to a polycystic kidney from 20XX-22 and underwent radical left nephrectomy with a diagnosis of RCC on 20XX-20, with no recurrence during follow-up. At the first visit, physical examination did not reveal any remarkable findings. Laboratory data did not show any abnormalities other than those due to hemodialysis (Table 1). As shown in Fig. 1, chest X-ray and CT scan revealed enlargement of the BHL with accumulation of fluorodeoxyglucose-positron emission tomography (FDG-PET) (Fig. 1-C). On CT (Fig. 1-D), a single small nodule was located in the left upper lobe without any tracer accumulation on FDG-PET. Magnetic

Abbreviations: BHL, bilateral hilar lymph nodes; CT, computed tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; FDG-PET, fluorodeoxyglucose-positron emission tomography; RCC, renal cell carcinoma.

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resonance imaging showed a single nodule with ring-like enhancement and edema in the right temporal and occipital lobes (Fig. 2-A, 2-B). Based on these imaging findings, we attempted to perform an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of the left hilar lymph node in November 20XX. However, because we found an intrabronchial mass that occluded the left lingular bronchus, we performed transbronchial direct biopsy (Fig. 3).

Histopathological findings from the biopsy specimens revealed clear cytoplasmic cells with a sinusoidal vascular network (Fig. 4-A). Immunohistochemical staining was positive for PAX8 and vimentin (Fig. 4-B, 4-C). Immunohistochemistry also revealed the following: AE1+AE3(+), CAM5.2(+), CD10(±), Naptin A(-), and TTF-1(-). The patient was diagnosed with extremely late recurrence of a clear cell type RCC. We confirmed that the finding was the same as that (Fig. 4-D) of the left nephrectomy specimen obtained on 20XX-20. The patient was transferred to a specialized facility for maintenance dialysis and renal cancer treatment. Brain radiotherapy and the combination anti-cancer therapy of avelumab and axitinib was initiated immediately.

3. Discussion

A recurrence developing for more than 10 years after the complete removal of the primary tumor is referred to as late recurrence [6].

The patient described herein experienced recurrence of BHL, lung, and brain metastases after a 20-year latent period. In a previous study [7], among 707 patients who underwent nephrectomy for RCC, the first relapse was reported to occur in the lungs (46.7%), bone (17.8%), retroperitoneal organs (11.1%), liver (6.7%), mediastinal lymph node (4.4%), and brain (2.2%). Miyao et al. [4] reported that among 470 patients who had undergone curative treatment of RCC and had not developed recurrence within 10 years of follow-up, 30 had developed late recurrence at 44 sites, including the lungs (36.4%), kidney (25%), and bone (13.6%), followed by the brain, pancreas, adrenal gland, lymph nodes, and liver.

To the best of our knowledge, there is no report of extremely late recurrence of RCC in both the BHL and brain 20 years after radical nephrectomy.

BHL enlargement is an important radiographic finding, and its incidence is reported to be 3–40 per 100,000 studies [8]. A previous study reported that the most common disease in 78 patients with bilateral and/or mediastinal lymphadenopathy diagnosed using EBUS-TBNA was sarcoidosis (73%), followed by lymphoma (10%) and reactive lymphadenopathy (10%); non-lymphoma malignancy was found in one case only [9]. This study speculated that RCC with BHL enlargement is extremely rare. In that study, lymph adenopathy was diagnosed by EBUS-TBNA in 92.3% of the cases [9]. Hence, EBUS-TBNA is an extremely useful modality for the diagnosis of BHL enlargement. The previous studies speculated two metastatic routes of RCC to the mediastinal hilar lymph node [10, 11]. One route [10] is through the retroperitoneal lymph node to the pulmonary ligament lymph node. The other route [11] is through the thoracic duct. Subsequently, malignant cells invading the retroperitoneal lymph node or the thoracic duct would settle in the mediastinal hilar lymph nodes.

The concept of tumor dormancy [12–14] is considered as a mechanism for late recurrence. Dormancy is thought to occur especially often in RCCs and cutaneous malignant melanomas [6] and is the stagnation of the cell cycle due to the non-proliferative phase of cancer cells and the extension of the quiescent phase [6]. It is speculated that the balance between immune function and tumor growth leads to dormancy [15]. It is thought that a decrease in immune function would trigger a reactivation in dormant lesions, which would subsequently appear as metastasis [16]. In this case, as the immune system declined with aging, RCC metastasis would have appeared.

A medical history of RCC thus warrants close attention from not only urologists but also the physician to assess the recurrence of RCC, regardless of the number of years after the surgery, even if the organ is the BHL, which is unlikely to be a relapse site of RCC. Physicians should maximally try to obtain the specimen from the organ for accurate diagnosis.

Table 1
Laboratory test on first visit.

Blood count		Biochemical test	
White blood cell (/μL)	4490	Aspartate aminotransferase (IU/L)	8
Neutrophil (/μL)	3228	Alanine aminotransferase (IU/L)	6
Lymphocyte (/μL)	561	Lactate dehydrogenase (U/L)	15
Eosinophil (/μL)	327	Total bilirubin (mg/dL)	0.3
Basophil (/μL)	31	Total protein (g/dL)	7.1
Red blood cell ($\times 10^4$ /μL)	285	Blood urea nitrogen (mg/dL)	38.5
Hemoglobin (g/dL)	9.2	Creatinine (mg/dL)	9.10
Platelet ($\times 10^4$ /μL)	20.6	Sodium (mEq/L)	138
Hemostasis test		Potassium (mEq/L)	4.4
Prothrombin time (sec)	11.7	Chloride (mEq/L)	100
APTT (sec)	28.8	C-reactive protein (mg/dL)	0.84
PT-INR	1.11	Tumor marker	
		CEA (ng/mL)	1.5
		CYFRA (ng/mL)	7.7
		ProGRP (pg/mL)	277.0

APTT: Activated partial thromboplastin time; PT-INR: Prothrombin time-international normalized ratio.

CEA: Carcino Embryonic Antigen; Cyfra: CYFRA: Cytokeratin-19 Fragment; ProGRP: Pro-Gastrin-Releasing-Peptide.

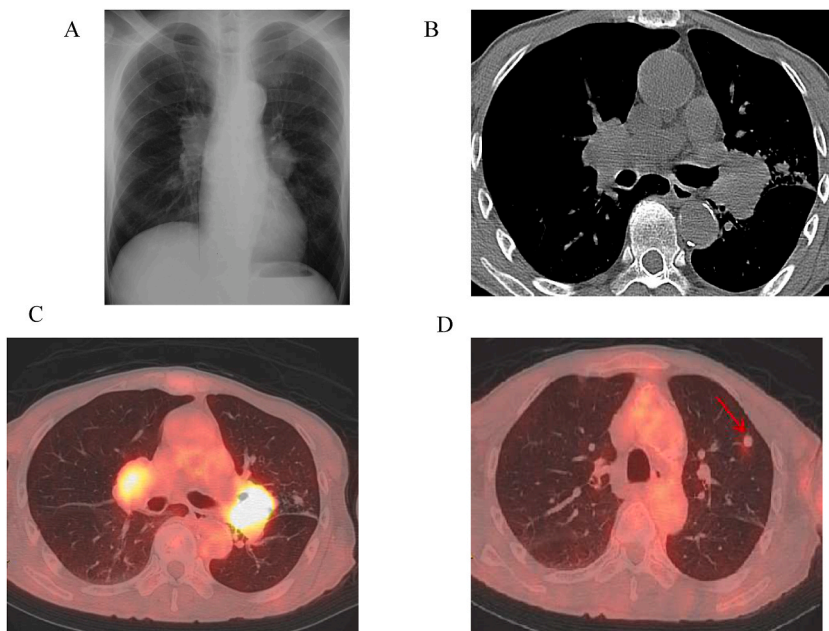


Fig. 1. A: Chest X-ray shows enlarged bilateral hilar lymph nodes (BHL) (arrows); **Fig. 1-B:** Chest computed tomography (CT) on mediastinum condition shows enlarged BHL (arrows); **Fig. 1-C:** a positron emission CT (PET) shows masses with accumulation in the BHL (arrows); **Fig. 1-D:** PET shows a single small nodule without accumulation in the left upper lobe of the lung.

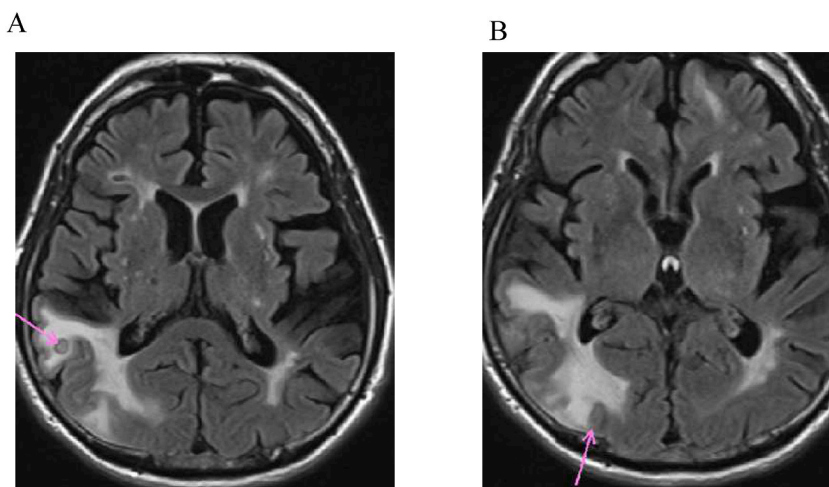


Fig. 2. A and B show magnetic resonance imaging indicating a single nodule with ring-enhanced image and edema in the right temporal and occipital lobe, respectively.

4. Conclusion

- 1) We reported a case of RCC with an extremely delayed relapse in both the brain and BHL 20 years after radical nephrectomy.
- 2) As the immune system declined with aging, dormant RCC metastasis would have appeared.
- 3) A medical history of RCC warrants close attention from not only urologists but also the physician to assess the recurrence of RCC, regardless of the number of years after the surgery, even if the organ is BHL, which is unlikely to be relapse site of RCC.

Ethics approval and consent to participate

We obtained written informed consent to publish the information, including the laboratory data and image findings, from the patient's family since the patient had already died at the time of writing this case report. Furthermore, this case report was approved by the Institutional Review Board of Ishikiriseiki Hospital on October 20, 2021 (approval number: 21–36).

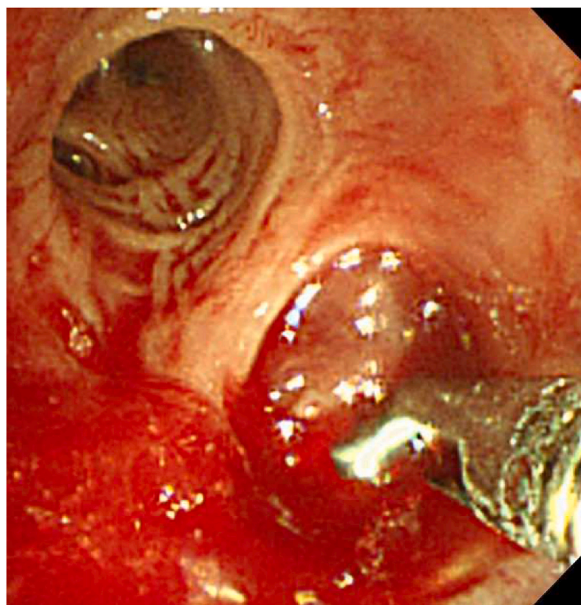


Fig. 3. shows an intrabronchial mass occluding the left lingular bronchus.

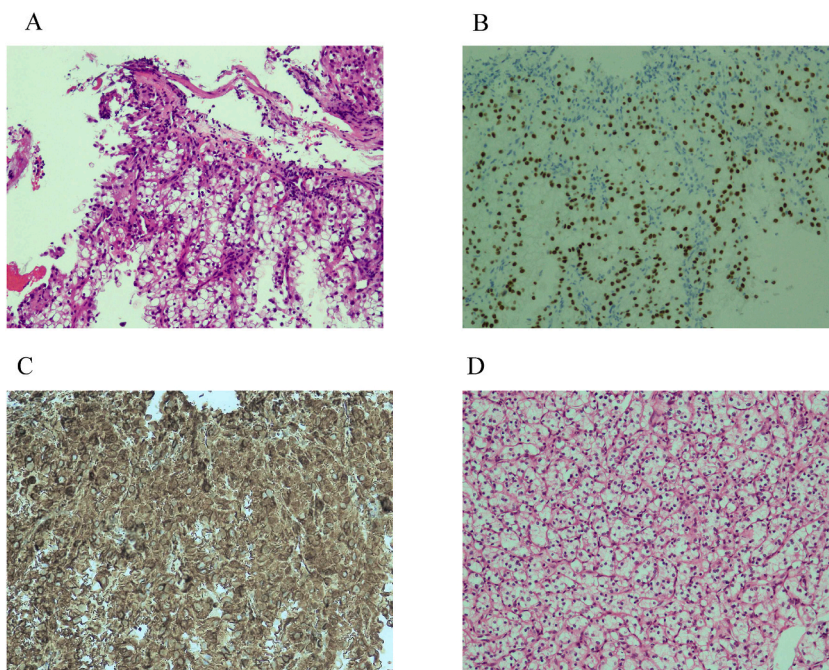


Fig. 4. Histological staining of specimens from the right hilar lymph node (A–C) and resected specimen of renal cell carcinoma (RCC) (D). (A) A photomicrograph of hematoxylin and eosin (H&E) staining of the endoscopic direct biopsy specimen reveals clear cytoplasmic cells mediated by a sinusoidal vascular network (magnification, x100). (B) Immunohistochemistry staining of the lymph node specimen showing positive PAX 8 (magnification, x100). (C) Immunohistochemistry staining of the lymph node showing positive vimentin (magnification, x100). (D) A photo micrograph of the H&E-stained resected specimen of RCC (magnification, x100).

Author contributions

Y.S., K.M., and T.H. conceived the outline plans. All authors contributed to the data interpretation. K.W. diagnosed the pathological findings. All authors read and critically reviewed the manuscript drafts. All authors have approved the final manuscript.

Declarations of competing interest

None.

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