

## Oncology

## Spontaneous regression of metastatic renal cell carcinoma after cytoreductive nephrectomy: A case report

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## ABSTRACT

We herein report a case involving a 59-year-old man with right lung and mediastinal lymph node metastases from renal cell carcinoma. After cytoreductive nephrectomy without neoadjuvant therapy, he achieved spontaneous regression. The regression was maintained 3 years after the operation. We immunohistochemically examined the surgical specimens and considered the possible mechanism underlying this phenomenon.

## Introduction

Spontaneous regression of metastatic renal cell carcinoma (mRCC) is rare but well-documented. The estimated frequency of this phenomenon is 1% of all cases of renal cancer. The mechanism underlying spontaneous regression of mRCC is unknown. Few reports of spontaneous regression have included immunohistochemical examination findings of the surgical specimens. We herein present a case of spontaneous regression of mRCC after cytoreductive nephrectomy (CN) without neoadjuvant therapy. We immunohistochemically examined the surgical specimens and considered the possible mechanism underlying this phenomenon.

## Case presentation

In April 2016, a 59-year-old man was diagnosed with mRCC following combined pulmonary fibrosis and emphysema. Enhanced computed tomography demonstrated a 17-mm-diameter nodule in the S2 site of the right lung (Fig. 1A), a 60-mm-diameter mass in a mediastinal lymph node (Fig. 1B), and a 62-mm-diameter mass in the left kidney. [<sup>18</sup>F]2-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) positron emission tomography showed high FDG uptake by these lesions.

The clinical diagnosis was mRCC, cT2aN1M1. The risk was considered intermediate according to the Memorial Sloan Kettering Cancer Center (MSKCC) risk classification and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model. The Karnofsky performance status was 80%. Laboratory tests revealed mild elevation of the C-reactive protein concentration at 6.52 mg/dL (reference range, ≤0.30 mg/dL); a normal corrected serum calcium

concentration, lactate dehydrogenase concentration, and platelet count; and a slightly low hemoglobin concentration at 13.0 g/dL (reference range, 13.5–17.6 g/dL). The levels of tumor markers, such as carcinoembryonic antigen and pro-gastrin-releasing peptide, were within the reference range. However, the cytokeratin 19 fragment concentration was 5.6 ng/mL (reference range, ≤3.5 ng/dL). The patient underwent laparoscopic CN with no complications in June 2016. The final pathological diagnosis of the renal tumor was clear cell RCC, G2, Fuhrman grade 2, pT3a (Fig. 2A). Moreover, we performed an immunohistochemical examination using CD4 (4B12; Novocastra Laboratories, Newcastle Upon Tyne, United Kingdom), CD8 (C8/144B; Dako, Glostrup, Denmark), and CD56 (CD564; Novocastra Laboratories, Newcastle Upon Tyne, United Kingdom). The examination revealed CD4 and CD56 expression was very weak (Fig. 2B and C). In contrast, lymphocyte infiltration into the primary lesion with CD8 expression (Fig. 2D).

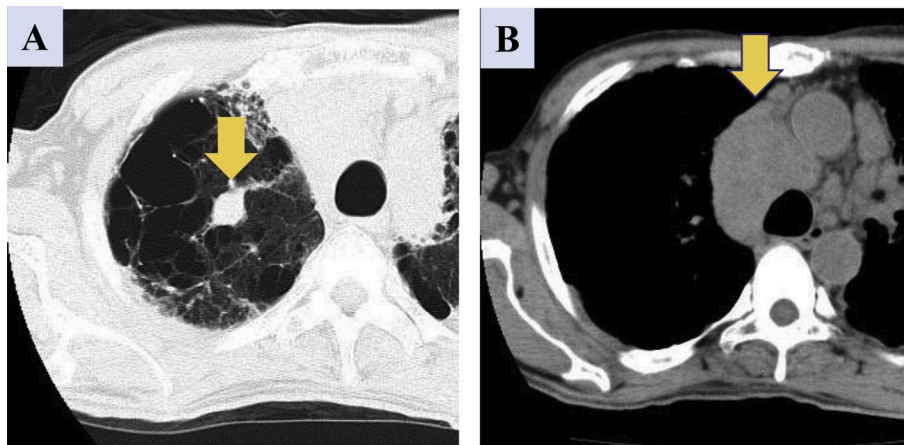
One month following surgery, a thoracic computed tomography scan revealed spontaneous regression of the pulmonary nodule and mediastinal lymph node, and both continued to decrease in size for 4 months. The pulmonary nodule and mediastinal lymph node then shrank from 17 to 6 mm (Fig. 3A) and from 60 to 31 mm (Fig. 3B), respectively, and spontaneous regression was still maintained 3 years postoperatively. Additionally, the cytokeratin 19 fragment concentration remained within the range of 4.3–5.3 ng/mL.

## Discussion

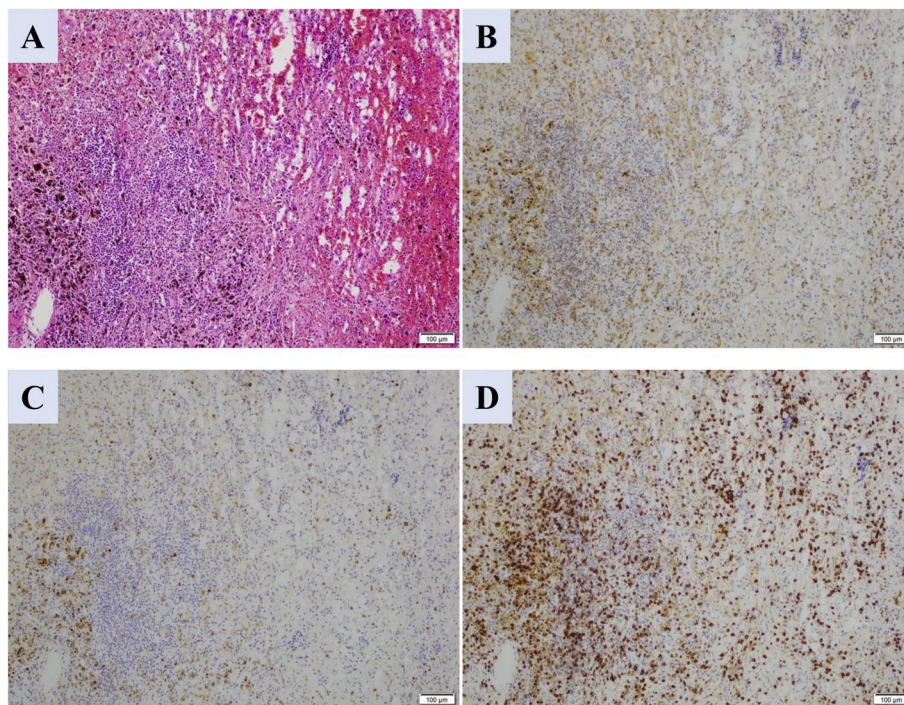
Spontaneous cancer regression is defined as remission or disappearance of the primary tumor tissue or its metastases in patients who

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**Fig. 1.** Enhanced computed tomography showed (A) a mass in the S2 site of the right lung and (B) a mass in a mediastinal lymph node.



**Fig. 2.** (A) Hematoxylin–eosin staining of a surgical specimen demonstrated clear cell carcinoma with lymphocyte infiltration. Immunohistochemical staining demonstrated the absence of (B) CD4 and (C) CD56 expression and (D) significant CD-8 expression.

have never been treated. Spontaneous regression of mRCC is rare but has been well-documented in patients with clear cell RCC, and it occurs in approximately 1% of all cases of renal cancer. Everson<sup>1</sup> divided spontaneous regression into four categories: primary tumor regression, metastatic tumor regression (with pathological diagnosis of the primary focus), metastatic tumor regression (no pathological diagnosis of the primary tumor), and radiologically considered metastatic tumor regression. The present CASE fits within the second and fourth categories.

The role of CN in the management of mRCC is controversial. In one study, CN followed by interferon- $\alpha$  treatment increased overall survival in patients with mRCC compared with immunotherapy alone.<sup>2</sup> In another study, CN provided an overall survival benefit in patients with a good performance status and good/intermediate IMDC/MSKCC risk classification of mRCC in the era of molecular-targeted therapy.<sup>3</sup> In the present era of systemic immunotherapy, CN plays an important role in the management of mRCC for well-selected patients.

Ikarashi et al.<sup>4</sup> reported a case involving a 59-year-old woman with mRCC who underwent CN after achieving a complete response of multiple lung metastases to neoadjuvant therapy using nivolumab following sunitinib. The surgical specimens showed high expression of PD-L1 in the tumor cells and infiltration of lymphocytes with CD8 expression by immunohistochemistry.<sup>4</sup> In another study, the surgical tissue samples of 756 patients with clear cell RCC who did not undergo immunotherapy were examined.<sup>5</sup> The results showed significantly higher densities of intratumoral T cells, cytotoxic T lymphocytes, and PD-1-positive immune cells in the clear cell RCC specimens with a response to immune checkpoint inhibitors than in the specimens with a mixed response or no response.<sup>5</sup>

Few reports of spontaneous regression of mRCC have described the immunohistochemical examination findings of surgical specimens without neoadjuvant therapy. We performed immunohistochemical staining of the surgical specimens in the present case. Immunohistochemical staining of CD4 was used as a general marker for helper T cells,

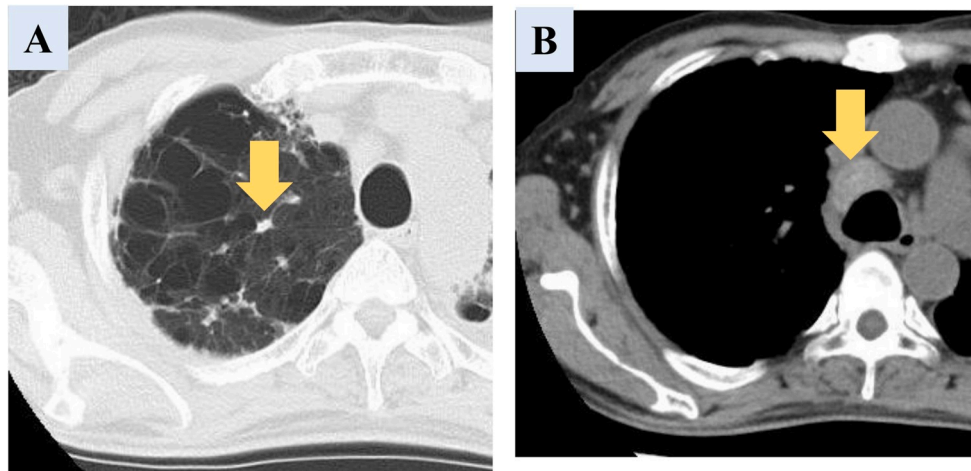


Fig. 3. Four months after surgery, computed tomography showed reduction of the (A) lung tumor and (B) mediastinal lymph node.

CD8 for cytotoxic T lymphocytes, and CD56 for natural killer cells. The staining results demonstrated lymphocyte infiltration into the primary lesion with CD8 expression. In contrast, CD4 and CD56 expression was very weak.

One mechanism underlying the immune response in patients with tumor rejection is that dendritic cells presenting tumor-associated antigens migrate to the lymph nodes, where they interact with T lymphocytes, activating CD8-positive cells. Nivolumab also enhances the activation of T cells and the cytotoxic effect of lymphocytes. In our case, infiltration of CD8-positive T cells into the tumor nest was advanced. We suspect that patients with spontaneous regression have already acquired antitumor immunity, and removal of the primary tumor enhances the biological defense system by reduction of the cancer antigen load.

### Conclusion

We have herein presented a case of spontaneous regression of mRCC after CN without neoadjuvant therapy. This case suggests that spontaneous regression is related to lymphocyte infiltration into the primary lesion with CD8 expression.

### Consent for publication

Not applicable.

### Funding

None.

### Authors' contributions

KM and TI performed the surgery. KM and YN drafted the manuscript. KM and TI finalized the manuscript. All authors have read and approved the final manuscript.

### Declaration of competing interest

None declared.

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### List of Abbreviations

CN	Cytoreductive nephrectomy
FDG	2-fluoro-2-deoxy-D-glucose
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
mRCC	metastatic renal cell carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center

### Ethics approval

This report was approved by the Ethics Committee of Tottori Prefectural Central Hospital (reference number 2017–60).

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