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Case Report

Pulmonary and liver metastases with repeated recurrence of renal epithelioid angiomyolioma after nephrectomy: one case report and literature review

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Abstract: Epithelioid angiomyolioma (EAML), a subtype of the family of perivascular epithelioid cell tumors (PEComas), is a relatively rare mesenchymal tumor with malignant potential including recurrence, vena caval invasion and distant metastasis. To date, there is yet no definite histopathological criterion for the malignant diagnosis. Positive expression of human melanoma black-45 (HMB-45) and Melan-A by immunohistochemical (IHC) staining may be critical for the identification of EAML. Here we described a case of a 42-year-old man who suffered malignant renal EAML of right kidney and underwent nephrectomy in 2009, but tumor relapsed in the affected renal region later in 2012 and the IHC staining of the involved lesion showed recurrent EAML after tumorectomy. Then he had event-free recovery for nearly 5 years. Nevertheless, in 2017, malignant neoplasms were detected in the left kidney and the right renal region once again, and multiple pulmonary and liver nudules were also observed by PET-CT examination. Through percutaneous lung biopsy, the pathology result of pulmonary nudules revealed malignant EAML, which was identical to the primary renal tumorous lesion. This paper presented a rare case of malignant renal EAML with repeated recurrence and multiple metastases during the 8 years after nephrectomy for the primary renal tumor.

Keywords: Epithelioid angiomyolioma, malignant tumor, renal, metastasis

Introduction

Angiomyolioma (AML) is a rare mesenchymal tumor which originates from perivascular epithelioid cells (PECs) and is recognized as a member of PEComas family [1]. Epithelioid angiomyolioma (EAML) is a monotypic type of AML, which is principally composed of proliferation of epithelioid cells with little adipose tissues [2]. About 24% patients with EAML possibly associate with history of tuberous sclerosis complex (TSC) [3]. Although EAML is usually considered to be a benign tumor, it occasionally can have aggressive biologic potential such as recurrence, local invasion and distant metastasis [4]. There are no histological criteria for malignant EAML. The positive expression of human melanoma black-45 by immunohistochemical (IHC) technology may contribute to the diagnosis of malignant EAML.

In this report, we described a case of a patient with renal EAML and repeated recurrence that multiple pulmonary and liver metastases were detected by PET-CT later in the 8th year after the initial nephrectomy. To the best of our knowledge, there are few reports on repeated recurrence of EAML in previous literatures. We discuss the clinicopathological characteristics, differential diagnosis, treatment option and prognosis as follows.

Case description

A 42-year-old man first presented in the hospital with a history of weight-loss for 10 kg within 6 months in 2009. An abdominal computed tomography (CT) scan showed a huge irregular soft tissue mass with uneven density in the right kidney, measuring 12.0 cm * 11.0 cm which occupied normal renal structure (**Figure 1**). The demonstration of the CT imaging

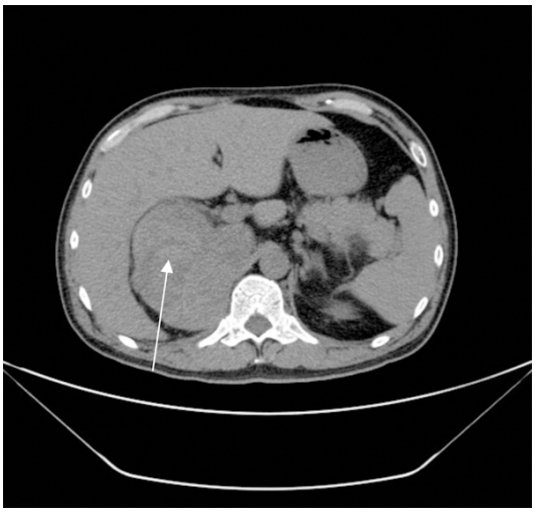

Figure 1. An abdominal computed tomography (CT) scan showed a huge irregular mass with uneven soft tissue density in the right kidney, measuring 12.0 cm * 11.0 cm (white arrow).

seemed to be a malignant renal tumor. The patient had no genetic family history of tuberous sclerosis complex or any previous medical history, and the laboratory test including blood tumor biomarkers and urine routine test showed no abnormal. Then the patient successfully underwent the right nephrectomy and the pathological analysis of the resected specimen was subsequently conducted. Microscopically, the carcinoma mainly consisted of polygonal epithelioid cells which solidly appeared with nest-like distribution and partial cells proliferated around the blood vessels. Morphologically, cellular atypia, nuclear heterogenity as well as patchy necrosis were demonstrated in majority of epithelioid cells, few adipose component was detected within smooth muscle components in marginal areas (**Figure 2**). The immunohistochemical staining revealed that the tumor cells were positive for HMB-45, Melan A, PAX-2, and negative for RCC together with low Ki67 labeling index (<5%) (**Figure 3**). Accordingly, the total results led to the final diagnosis of renal EAML.

Then the patient was advised to our hospital for the yearly follow-up visit, and he had no renal recurrence over nearly 3 years. In 2012, an ultrasound examination of urinary system detected an abnormal mass measuring 11.0 cm * 10.0 cm was detected in the affected right renal region. Consequently, tumorectomy

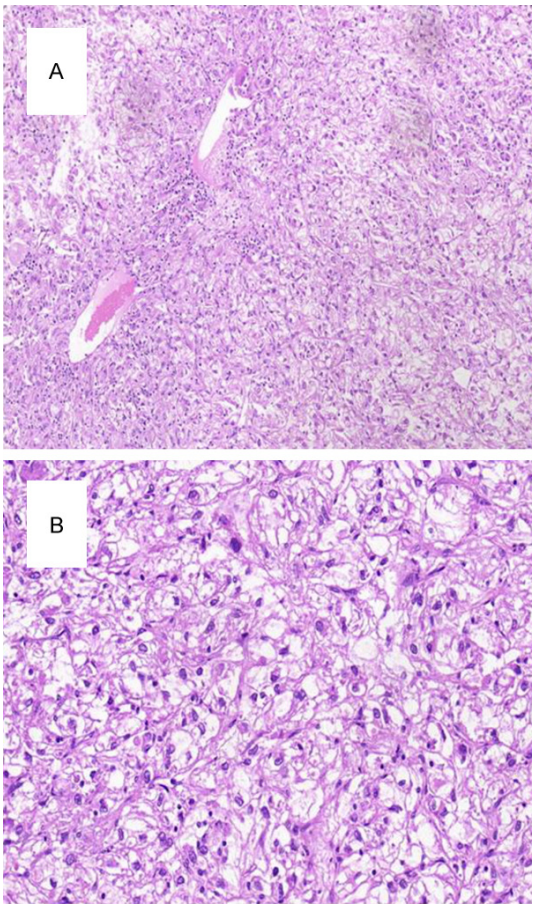

Figure 2. Histopathological findings of the renal EAML. A. Microscopically, the tumor was mainly composed of heteromorphic epithelioid cells and blood vessels. (hematoxylin and eosin; magnification, ×100). B. The epithelioid cells displayed cellular atypia and nuclear heterogeneous with nest-like distribution. (hematoxylin and eosin; magnification, ×400).

was performed with respect to the involved renal region. Remarkably, the final result of IHC staining showed the recurrent epithelioid angiomyolioma. Then the patient experienced unevenly recovery for 5 years. In 2017, two retroperitoneal neoplasm located in the bilateral kidney region was observed by an abdominal CT scan. The PET-CT examination was then carried out to assess the general condition. The findings of PET-CT scan showed a soft propensity mass, sized 10.0 * 10.7 * 9.0 cm, slightly above the right renal region with accumulated ^{18}FDG uptake (SUVmax 4.8), and a lobulated mass measured 6.5 * 6.9 * 6.9 cm in the middle-upper left kidney (SUVmax 4.5), accompanied with many enlarged small lymph nodes in

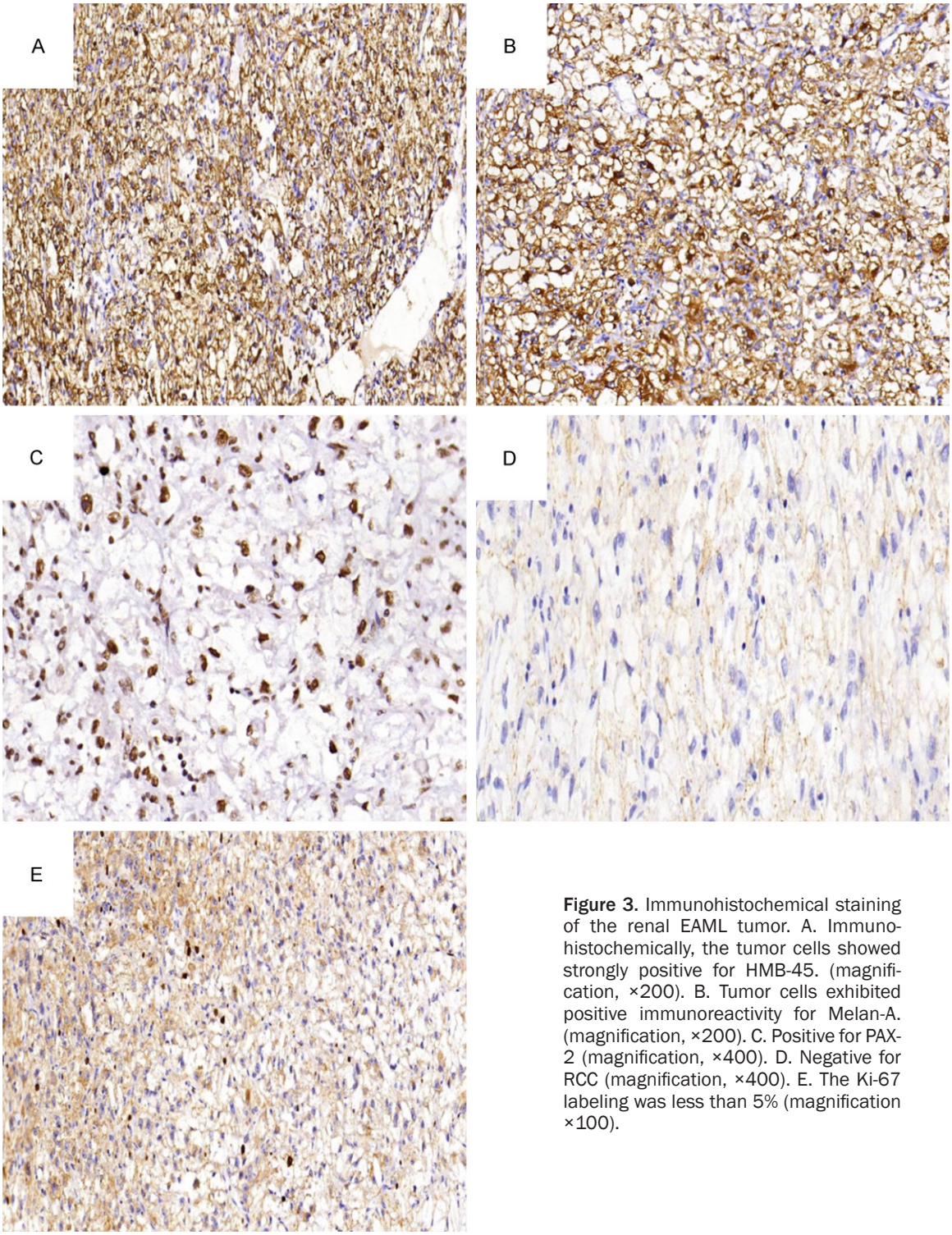

Figure 3. Immunohistochemical staining of the renal EAML tumor. A. Immunohistochemically, the tumor cells showed strongly positive for HMB-45. (magnification, ×200). B. Tumor cells exhibited positive immunoreactivity for Melan-A. (magnification, ×200). C. Positive for PAX-2 (magnification, ×400). D. Negative for RCC (magnification, ×400). E. The Ki-67 labeling was less than 5% (magnification ×100).

the posterior peritoneum (**Figure 4**). Furthermore, some well-defined lesions with high SUV were also found in inferior lobe of the left lung and right lobe of the liver, respectively. Through percutaneous lung biopsy, the pathology result of pulmonary nudules revealed malignant EAML which was similar to the primary renal tumor (**Figure 5**). Thus we determined that renal EAML replased with multiple pulmonary and liver metastases. The patient is currently in stable

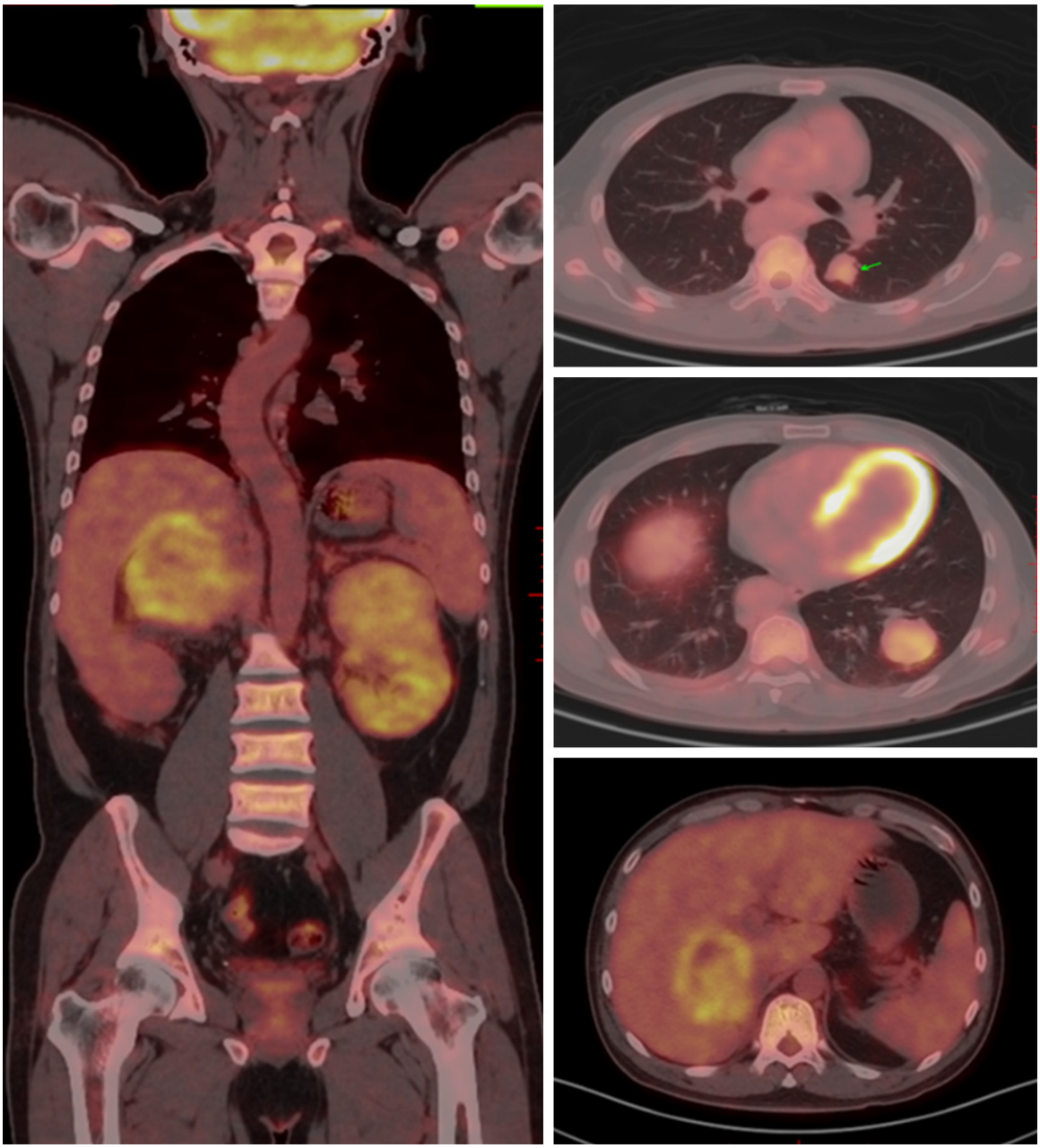

Figure 4. The PET-CT examination demonstrated two huge solid mass with accumulated ^{18}FDG uptake in the middle-upper left kidney and above the right renal region respectively, accompanied with some enlarged lesions in the lung and the liver.

condition since the treatment of mTOR inhibitor *everolimus* for two months.

Discussion

Epithelioid angiomyolioma was firstly described as a rare variant of AML which stemmed from mesenchymal tissue by Pea et al. in 1998 [4]. It belongs to a family of PEComa characterized by the prominent proliferation of epithelioid cells. Kidney, retroperitoneal and liver are the common sites which angiomyolioma usually originates from [5]. EAML has two clinical forms that either sporadically occurs or syndromically associates with TSC [6], and the occurrence of epithelioid AML has female predominance (80%) [7]. In contrast to classical AML, EAML has a younger age and a larger-sized tumor in the traits of mordity [8]. Some studies [2, 9, 10] suggested that tumor >5 cm in diameter might

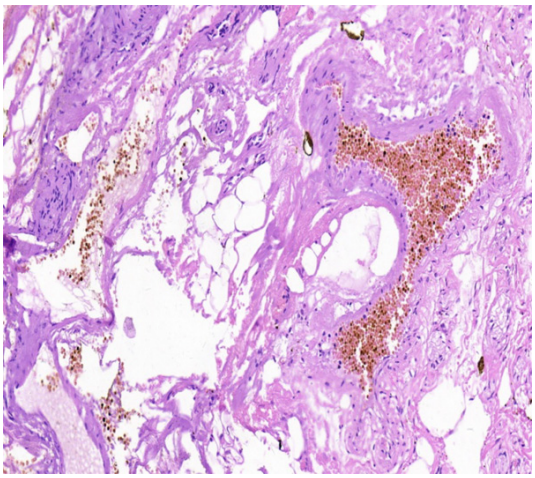

Figure 5. Histopathological findings of the recurrent EAML in the lung. The epithelioid neoplastic cells were positive for HMB-45 by immunohistochemical staining, which were similar to those of the primary renal EAML tumor. (magnification, ×100).

have malignant potential, which was also in compliance with our finding. Unlike classical AML as a benign tumor, one-third of EAML have aggressive biological features such as local recurrence, vascular invasion and metastases. Although some researchers considered distant metastases as an only definite evidence of malignancy [11], rapid progression and invasion to vena cava and lymphvessel were also believed to be potential aggressive forms.

In the present case, the diagnosis of malignant EAML was confirmed on the basis of tumor locoregional occurrence and multiple metastases. Fukuda et al. reported one case of malignant hepatic EAML which relapsed in the lung 7 years after hepatectomy [12]. In our case, the patient suffered renal EAML with a longer course for nearly 8 years. Nonetheless, the tumor repeatedly occurred in the initial region although tumor resection had been actively performed, which was scarcely reported in the previous literatures. The mechanism of tumor recurrence remained unclear. We hypothesized that some functional chemokines homologous to kidney may involve in the pathogenesis of renal EAML relapse. Further work will be necessary to confirm the idea.

Histopathologically, there are no definite criteria for the diagnosis of malignant EAML. Under microscopic examination, polynuclear cells, nuclear atypia, necrosis and high mitosis figures are regarded as predictive signs of malignant phenotype [13]. The exhibition of cytologic atypia and necrosis has been reported in many cases [14-16], that was also true of ours. In terms of IHC, epithelioid cells were focally positive for metanocytic markers (HMB-45, Melan A), smooth muscle markers (SMA) and Vimentin. Recently, Konosu-Fukaya et al. suggested that E-cadherin and β-catenin may be essential markers for the detection of renal EAML, and indicated the IHC results may reveal the activation of mTOR1 pathway [17].

Renal cell carcinoma (RCC) is the main differential diagnosis, which often challenges the consideration of EAML owing to the imaging similarity on CT [18]. Radiologically, small abundance of fat can be found with the borders of RCCs that invade renal sinus fat and liposarcomas whereas poor adipocytes appear in malignant EAML. This may aid to distinguish EAML from RCCs. In the present case, heterogeneous enhancement of the tissue density was observed in the irregular renal tumor on CT images. Additionally, PET-CT revealed multiple FDG accumulation in renal, lung and liver, indicating the widespread of tumor cells which further confirmed the malignancy. Remarkably, the inferior vena cava (IVC) is accessible to the primary lesion area on coronal scanning, so we speculated that tumor cells probably spread into the opposite kidney, lung and liver via invasion to IVC with suspected tumor thrombus. Moreover, the uptakes of renal, lung and liver sites were not very high and their values were similar. This raised a thought-provoking issue: is it the malignant renal EAML with multiple metastases or purely multicentric EAML? It deserved discussion and more tasks need to be conducted.

The treatment strategy for EAML is of importance and often depends on radiographic size and clinicohistological features [19]. Radical nephrectomy is recommanded if tumors are >4 cm and partial resection if not. Actually, surgical resection is the gold standard treatment for EAML due to its malignancy, and facilitates the differentiation between EAML and RCC by postoperative pathology. Although some patient have good prognosis after surgical treatment [20], local recurrence and metastases have also been reported including our case. In addition, chemotherapy for malignant EAML is another option because of its chemosensitiviy.

EAML has been reported to respond to doxorubicin. Recently the activation of rapamycin (mTOR) pathway has been found to involve in the pathogenesis of EAML, providing a novel therapeutic target. The utilize of an rapamycin (mTOR) inhibator such as everolimus has acquired benefits in the treatment of EAML [21]. In the present case, the patient was treated with everolimus since he was encountered with distant metastases in lung and liver. At the moment, the general state of the patient was under the control after two months of treatment with everolimus.

In summary, we reported a case of malignant renal EAML with repeated recurrence and pulmonary and liver metastases after the initial nephrenomy. EAML is an equivocal tumor on account of potential aggressive behaviors and there are no histopathological criteria for the malignancy. HBM-45 staining may contribute to the differentiate diagnosis. Surgical resection is the preferred therapeutic option and most patients have good survival rates. If regional occurrence and distant metastases take place, renal EAML often have poor prognosis, therefore a regular follow-up is indispensable after the initial nephrectomy.

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Disclosure of conflict of interest

None.

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