Clinical Features of de Novo Lung Neuroendocrine Tumor after Liver Transplantation for Hepatocellular Carcinoma

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Abstract: *Objective*: To analyze the clinical features of de novo lung neuroendocrine tumor (NET) after liver transplantation (LT) for hepatocellular carcinoma (HCC).

Method: Retrospectively reviewed the clinical data of the 1253 patients who underwent LT from 2013 to 2022 in our institute.

Result: Out of 1253 recipients of LT 7 patients suffered de novo lung carcinoma, of these 2 patients suffered lung NET accounting for 28.6% (2/7) of de novo lung carcinoma both at extensive stage. New on-set lung lesions and hilar and mediastinal lymphadenopathy were found by imaging tests; and were diagnosed as lung NETs in both patients through pathological examination. The interval between LT and diagnosis of lung NET ranged from 5.9 to 44.7 months. Both patients received cisplatin and etoposide as first-line chemotherapy and achieved partial remission. The progression-free survival period ranged from 1.9 to 2.2 months. Survival after diagnosis of lung NET ranged from 7.0 to 10.9 months. One of the patients tried to cease immunosuppressants during chemotherapy and incurred graft rejection.

Conclusion: Lung NET may have a higher proportional incidence of de novo lung carcinoma in LT recipients. Early diagnosis is vital for the treatment of lung NET, while predictive and timely biopsy based on imaging findings is crucial for making an early diagnosis.

Keywords: Lung neuroendocrine tumor, liver transplantation, hepatocellular carcinoma, clinical features, early diagnosis, pathological biopsy, differential diagnosis.

INTRODUCTION

Liver transplantation (LT) has been an effective therapy choice for selected patients with hepatocellular carcinoma (HCC). Nevertheless, malignancies after LT including recurrent HCC and de novo malignancies are among the leading causes of death in transplant recipients who receive long-term immunosuppression and may have an elevated risk of malignancies [1-4]. The overall incidence rates of de novo malignancies after LT have been reported to be 5% to 16% [5] and the incidence rates of de novo lung cancer can be 0.6%-1.2% [6]. Compared with de novo malignancies, HCC recurrence or metastasis is more common. Actually, previous studies have reported the incidence rate of HCC recurrence to be about 11% to 26% in recent decades and lung is the most common site of recurrence or metastasis [7-13]. In this case, new lung lesions after liver transplantation for HCC may be easily associated with metastases of HCC. However, de novo malignancies after LT are not unusual in fact, especially when compared with the matched general population. Several studies have reported that the incidence rate of de novo lung carcinoma in LT patients can be about 2-8 times of the rate in general population [6, 14]. Moreover, more than 70% of lung cancers after transplantation were detected at TNM stage IV, indicating a poor prognosis [5, 15-17]. If an incorrect or untimely diagnosis was made, the best treatment window would be missed and therapeutic results would be worse.

Lung neuroendocrine tumor (NET) is a special type of lung carcinoma with varied malignant degrees. Some subtypes of lung NET can be very aggressive, such as small cell lung carcinoma (SCLC), which is the most common lung NET with rapid tumor growth, high metastasis, and dismal clinical outcomes [18, 19]. Although SCLC is highly sensitive to chemotherapy and radiotherapy, the recurrence rate is fairly high and the average survival time is short [20]. Besides, during the past 30 years very little improvement in therapy for SCLC has been achieved making it a refractory cancer [21]. The situation may get even worse under the conditions with chronic immunosuppression such as after liver transplantation. But, the study of lung NET or SCLC after liver transplantation is scarcely available in literature. Therefore, we aimed to study the characteristics of lung NET in patients who received LT for HCC.

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MATERIALS AND METHODS

Clinical Case Inclusion

We retrospectively analyzed the clinical data of patients who suffered de novo primary lung NET after LT for HCC from January 2013 to January 2022 in the First Affiliated Hospital of Sun Yat-sen University. This study was approved by the Clinical Research Ethics Committee of the institute. Presence of Lung carcinoma prior to liver transplantation were excluded by imaging tests and negative serum cancer biomarkers such as CEA, SCC and CA199.

Surgery and Immunosuppressive Regimen

All patients received orthotopic liver transplantation. Multiple or combined organ transplantation was excluded. Tacrolimus was used as the basic immunosuppressive drug after LT. The valley concentration of Tacrolimus was 6-10 ng/L in long-term follow-up. Other immunosuppressive drugs including Sirolimus and Everolimus were also used in which case the dose of Tacrolimus was reduced.

Laboratory and Imaging Investigations

Laboratory tests, including blood cell count, biochemistry, liver function, Tacrolimus concentration and serum cancer biomarkers such as AFP, were routinely assessed for graft function management and tumor surveillance. After LT, chest and abdomen CT scan were performed every 3-6 months in the first year and every 6-12 months afterward or when necessary. For suspicious malignancy, the whole-body PET-CT was performed.

Biopsy and Pathological Examination

When acute graft rejection is suspected, a graft liver biopsy should be done for pathological diagnosis. For suspected new on-set malignancy, including intrahepatic and extrahepatic lesions, puncture biopsy and pathological examination should also be performed. Immunohistochemistry staining can be used when diagnosis is difficult.

The diagnosis of lung NET was confirmed by pathological examination including HE and immunohistochemistry staining.

RESULTS

Basic Information

Total 7 patients suffered de novo lung carcinoma within 1253 recipients of LT. All patients were male and ranged in age from 51 to 70 years old when diagnosed with lung cancer. The pathological types of these new on-set lung carcinoma included adenocarcinoma, squamous cell carcinoma and lung NET. Two patients were diagnosed as lung NET accounting for 28.6% (2/7) of de novo lung carcinoma; and included in our study. Ages of both patients were between the range of 49 to 52 years when diagnosed with lung NET. Both received allogeneic liver transplantation for HCC and decompensated liver cirrhosis and had a high level of AFP before the operation. The first patient suffered alcoholic cirrhosis and fasciola hepatica, and the second one suffered Hepatitis B cirrhosis. Both patients had bleeding from esophageal or gastric varices and were treated with endoscopic ligation hemostasis several years before LT. The first patient received splenectomy and pericardial devascularization for portal hypertension and transarterial chemoembolization (TACE) and ablation therapy for HCC before LT. The second patient had a history of hypertension and diabetes.

Clinical Findings

The clinical findings and prognosis of both patients are shown in Table **1**. The intervals between LT and diagnosis of lung NET were 44.7 months and 5.9 months, respectively. Multiple lesions in unilateral lung and hilar and mediastinal lymph nodes were found in both patients at the first diagnosis. Both were given cisplatin and etoposide as first-line chemotherapy and achieved partial remission. The progress-free survivals were 1.9 months and 2.2 months, respectively. The survivals after diagnosis of lung NET were 10.9 months and 7.0 months, respectively. The second patient received second-line chemotherapy that composed of paclitaxel (albumin-bound) and carboplatin and external radiotherapy and percutaneous Iodine 125 particles implantation for lung and hilar mediastinal lesions after lung cancer progression.

Both patients continued to use immunosuppressants after suffering from lung cancer. Everolimus was used and dosages of Tacrolimus were reduced in both patients. The second patient tried to cease using immunosuppressants during the first cycle of second-line chemotherapy. Graft rejection occurred only about 1 month after drug withdrawal, and corticosteroids and Tacrolimus had to be used again to treat the rejection.

AFP dropped to normal range after LT in both cases. For the second patient, AFP was found to

Table 1: Clinical Findings and Prognosis of Patients with Lung NET after LT

	Patient 1	Patient 2
Interval between LT and lung NET	44.7 months	5.9 months
NET Sites at diagnosis	lung; hilar and mediastinal lymph nodes; pleura;	multiple lesions in lung; hilar and mediastinal lymph nodes
NET Staging at diagnosis	extensive stage	extensive stage
Progress-free survival	1.9 months	2.2 months
Survival	10.9 months	7.0 months
First-line chemotherapy	cisplatin + etoposide, 3 cycles	cisplatin + etoposide, 2 cycles
Second-line chemotherapy	N/A	paclitaxel (albumin-bound) + carboplatin, 1 cycle
External radiotherapy	N/A	Applied
Internal radiotherapy	N/A	Applied
Immunosuppressant withdrawal	N/A	Applied
Graft rejection	N/O	Occurred
Lung metastases of HCC	N/O	Occurred
Recurrent HCC in graft liver	N/O	Occurred
TACE	N/A	Applied
RFA	N/A	Applied
Lenvastinib	N/A	Applied

N/A: not applied; N/O: not occurred; TACE: transcatheter arterial chemoembolization; RFA: radiofrequency ablation.

increase again about 4 months after LT, and multiple lung lesions were also found and diagnosed as metastases by imaging examination. Lenvastinib was given and percutaneous Iodine 125 particles implantation was performed for these lung lesions. AFP declined but rose gradually afterward. During the second cycle of first-line lung cancer chemotherapy, intrahepatic recurrence was found in the graft liver. The patient received TACE and RFA for recurrent HCC and recovered soon before the next cycle of chemotherapy.

Findings on Imaging of the Lesions

New on-set lung lesion of the first patient was first found in a routine follow-up CT scan, with the size about 4.0 cm in diameter, irregular edge and moderate enhancement (Figure **1a**). The lesion was located at the dorsal bronchus of the left lower lung which was surrounded and occluded by the lesion, while a few nodular and strip-shaped satellite foci could be seen around the lesion (Figure **1b**). Lymphadenopathy in left hilum and mediastinum (Figure **1c**) as well as left pleural effusion (Figure **1a**) could also be seen. Meanwhile, a small lesion about 1.2 cm in diameter in the right upper lung was found with adjacent pleural traction and surrounding satellite foci and tortuous strip shadows (Figure **1d**). The following PET-CT revealed elevated glucose metabolism and positive somatostatin receptor in the left thoracic lesions (Figure **2a**, **b**). The lesion in the right upper lung was also found to have elevated glucose metabolism and weakly positive somatostatin receptor (Figure **2c**, **d**). Combining the results of imaging tests, the diagnosis of lung NET was established.

In the second patient, new on-set lung lesions were first identified by routine CT scan about 7 weeks before diagnosis of lung NET, in which multiple lung solid nodules were found in the right lung with a maximal size of 0.6 cm in diameter and slightly increased glucose metabolism (SUVmax 1.6) (Figure **3a-d**). In addition, several lymph nodes in right hilum and mediastinum were found to have slightly increased metabolism (Figure **3e**). In view of the coexistence of lung metastasis and the increase in AFP, percutaneous Iodine 125 particles implantation seeds into the lung combined with Ievastatin were performed. About 7 weeks later, lymph nodes in hilar and mediastinum were found to be enlarged with increased metabolism (SUVmax 5.2, maximum diameter 2.6 cm) (Figure **4a-d**). More pulmonary lesions appeared near right

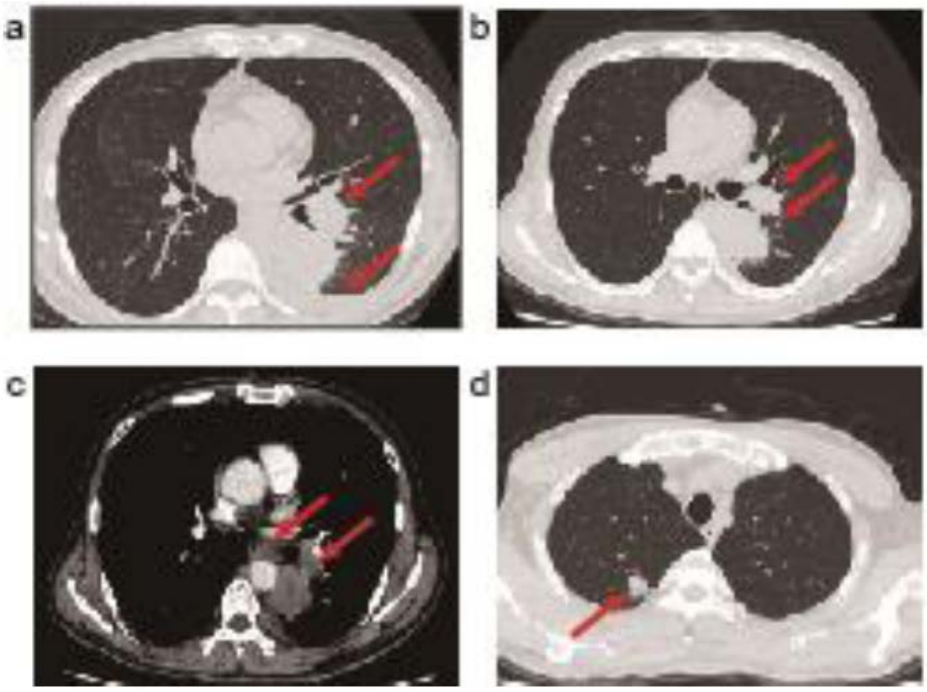

Figure 1: CT manifestations of new on-set lung lesions of patient 1. **a**. About 4cm in diameter, irregular edge and moderate enhancement of the lesion in the dorsal segment of left lower lung and the left pleural effusion could be seen. **b**. The dorsal bronchus of the left lower lung was surrounded and occluded by the lesion with a few nodular and strip-shaped satellite foci around the lesion. **c**. Lymphadenopathy in left hilar and mediastinum. **d**. Lesion in the right upper lung about 1.2 cm in diameter with adjacent pleural traction and surrounding satellite foci and tortuous strip shadows.

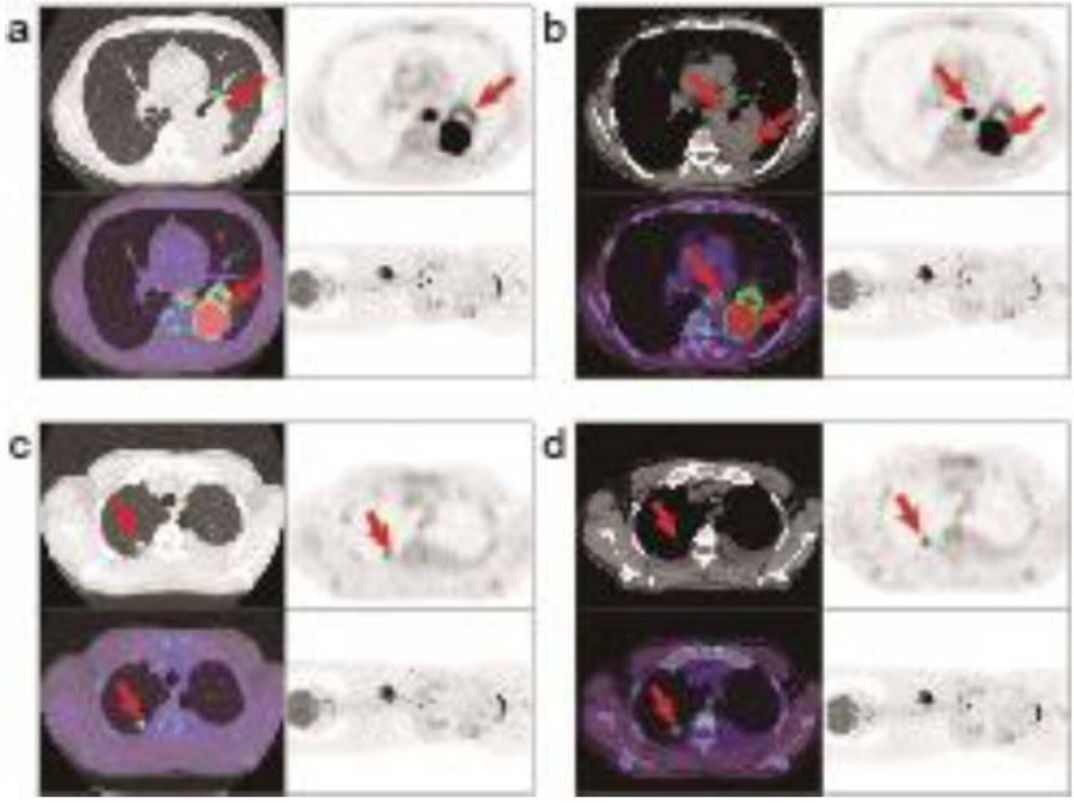

Figure 2: PET-CT manifestations of new on-set lung lesions in patient 1. **a-b**. Elevated glucose metabolism (a) and positive somatostatin receptor (b) in the left thoracic lesions. **c-d**. Elevated glucose metabolism (c) and weakly positive somatostatin receptor (d) in the lesion in the right upper lung.

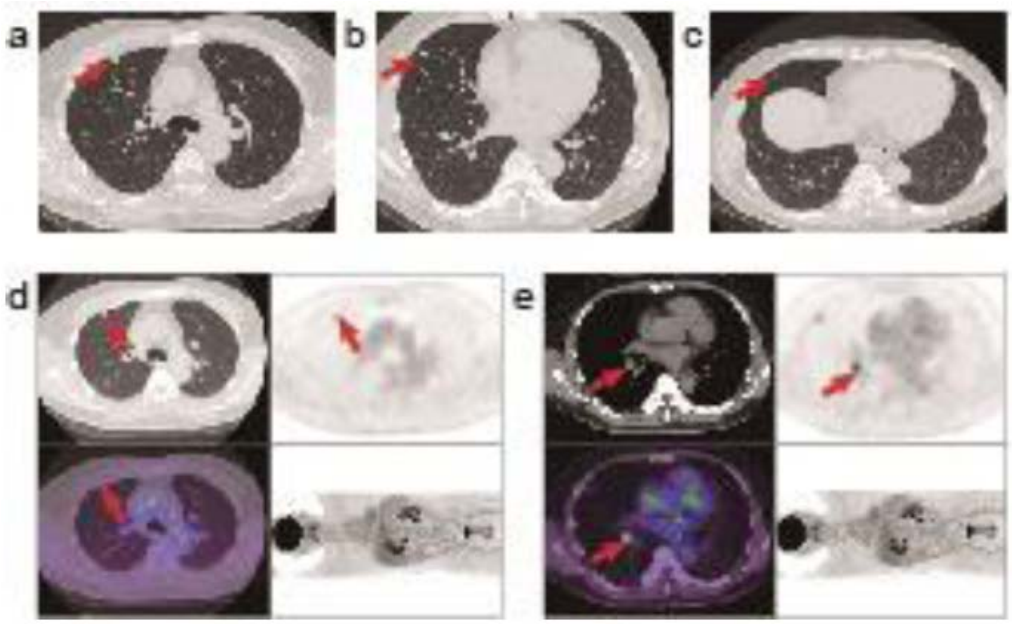

Figure 3: Imageological findings of new on-set lung lesions of patient 2 about 7 weeks before diagnosis as lung NET. **a-b**. Solid nodules in the right upper lung with a maximal size of 0.6 cm in diameter. **c.** Solid nodule in the right middle lung. **d**. Slightly increased glucose metabolism (SUVmax 1.6) in the lung lesion in the right upper lung. **e**. Slightly increased metabolism (SUVmax 3.9, maximum diameter 0.5 cm) in lymph nodes in right hilar and mediastinum.

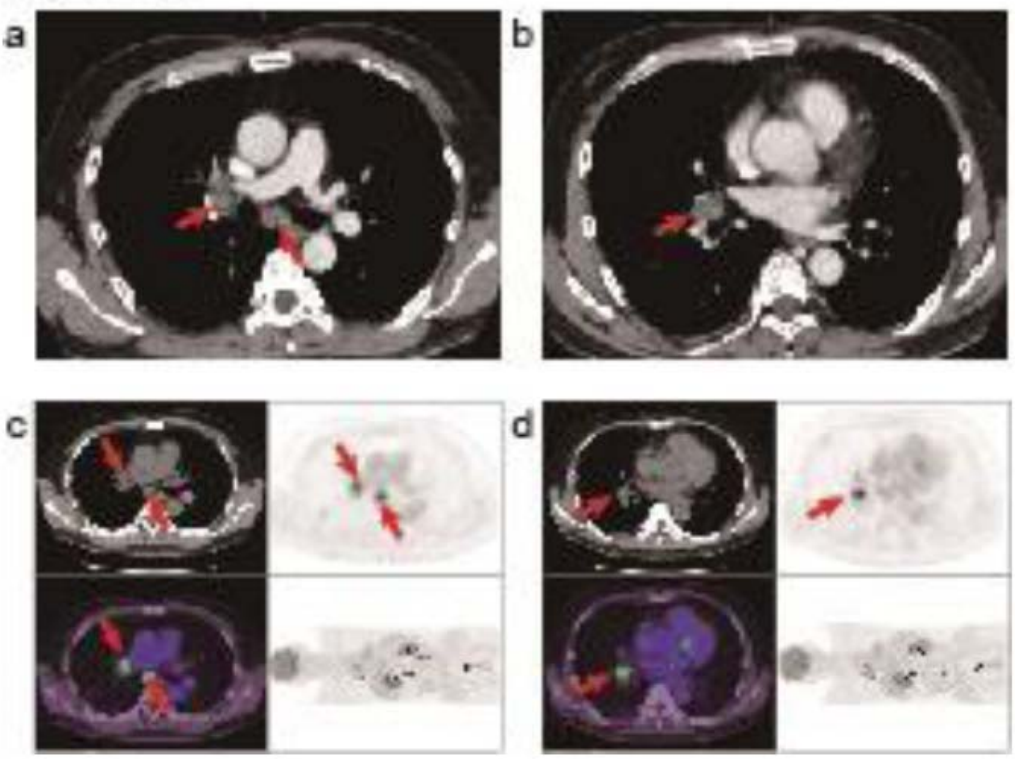

Figure 4: Findings on Imaging of lesions in hilar and mediastinal lymph nodes, diagnosed as lung NET in patient #2.

horizontal fissure which were spot, strip and flake like in shape with slightly increased metabolism (SUVmax 1.9), as well as in right lower lung (Figure **5a-d**). The imaging diagnosis of primary lung carcinoma was still difficult until the following pathological results came out.

Pathological Findings

Lung lesion biopsy was performed in the first patient while hilar and mediastinum lymph nodes biopsy was conducted in the second patient. Both patients were

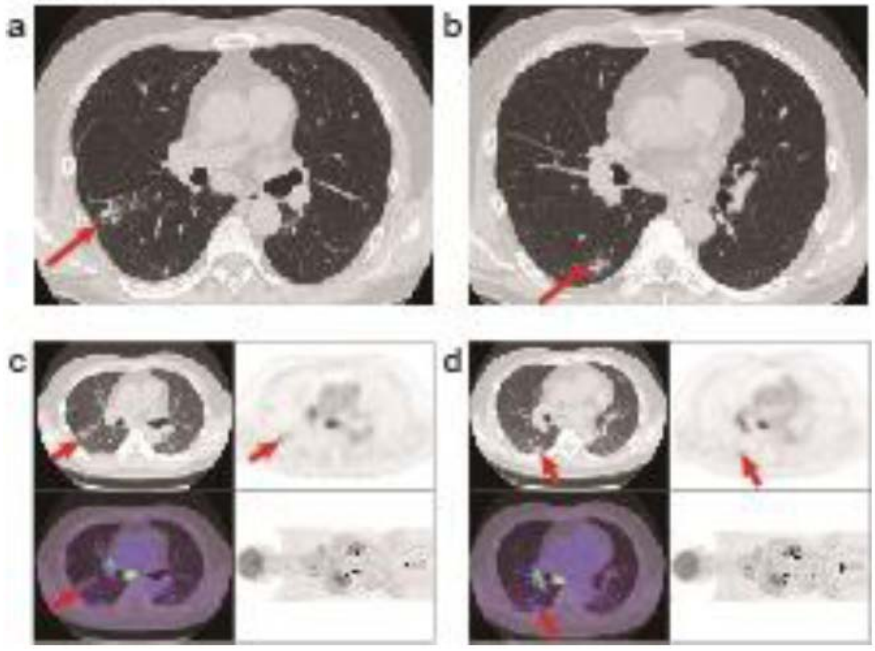

Figure 5: Findings on Imaging of lesions in lung, diagnosed as lung NET in patient # 2. (**a**) Lung lesions near right horizontal fissure spot, (strip and flake like in shape); with slightly increased metabolism (SUVmax 1.9) (**c**). (**b**) Lung lesion in right lower lung; with slightly increased metabolism (**d**).

preliminarily diagnosed as lung NET by HE staining and confirmed by immunohistochemistry staining, differentiating from hepatocellular carcinoma. The HE staining findings of both patients are shown in Figures **6** and **7**. In the first patient, the tumor tissue showed nest-like infiltration and local tumor necrosis, while the tumor cells were characterized by small cells with large nucleocytoplasmic ratio and obvious atypia. In the slide of the second patient, small tumor cells were distributed in flakes or in scatter, with large nucleocytoplasmic ratio, deeply stained nuclei or fine chromatin and inconspicuous nucleolus. Karyokinesis, tumor giant cells and multifocal tumor necrosis can be seen and the atypia was obvious. The immunohistochemistry results of both patients are shown in Table **2**.

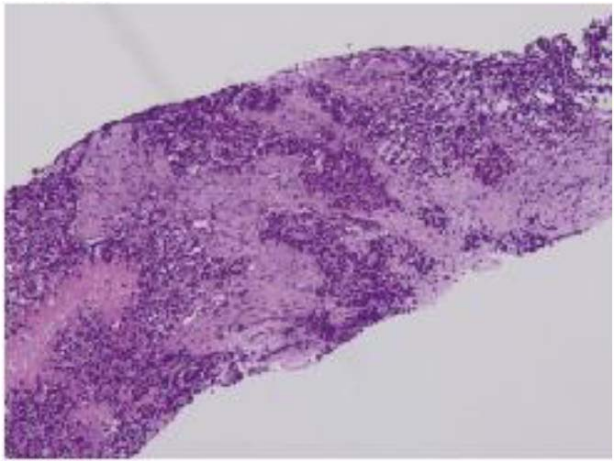

Figure 6: HE staining findings of lung lesion biopsy of patient 1. The tumor tissue showed nest-like infiltration and local tumor necrosis, while the tumor cells were characterized by small cells with large nucleocytoplasmic ratio and obvious atypia.

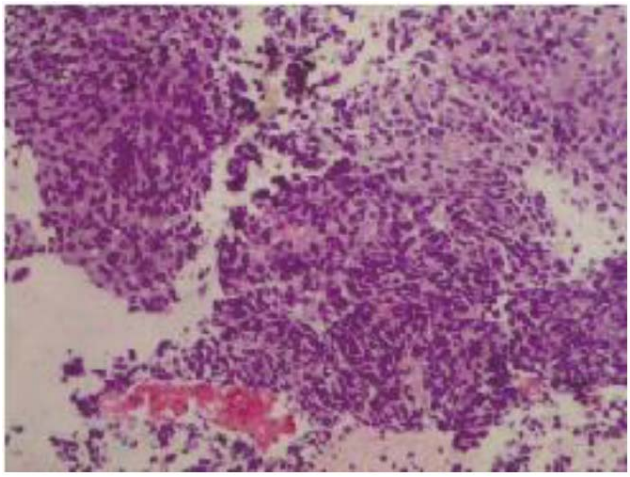

Figure 7: HE staining findings of hilar and mediastinum lymph nodes biopsy of patient 1 when diagnosed as lung NET. Small tumor cells were distributed in flakes or in scatter, with large nucleocytoplasmic ratio, deeply stained nuclei or fine chromatin and inconspicuous nucleolus. Karyokinesis, tumor giant cells and multifocal tumor necrosis can be seen and atypia was obvious.

DISCUSSION

Lung neuroendocrine tumor (NET) is a relatively rare tumor and its most common subtype, small cell

lung carcinoma (SCLC), however, is an aggressive malignant tumor with poor prognosis and the mechanism of its occurrence is still unclear. It has been reported that SCLC accounted for 13-15% of all lung cancer cases in recent years [22]. Herein, we analyzed clinical data of LT recipients in our center in last 10 years and found the proportional incidence of lung NET can be as high as 28.6% of all de novo lung carcinoma in LT recipients. The association between the development of lung NET and long-term immunosuppression after LT deserves attention. Besides, new-onset lung lesion after LT for HCC, such as lung metastasis, is more common thus making lung NET easily be ignored and more difficult to be diagnosed.

Differential Diagnosis of New Lung Lesions after LT for HCC

Imaging examinations including contrast-enhanced CT or MRI at regular intervals after LT for HCC are often recommended in the surveillance of recurrence and extrahepatic metastasis of HCC [23-25]. Serial AFP tests are also useful to monitor recurrence for patients who had an elevated AFP prior to LT [23]. In some cases, however, the imaging manifestations of new-onset lung lesions may be atypical and the rebound of AFP may not be significant, thus, distinguishing between HCC metastasis and primary lung cancer becomes challenging [26-28]. In our study, new-onset lung lesions in the second patient associated with mildly increased AFP, were firstly diagnosed as lung metastasis. The patient received Lenvastinib and percutaneous Iodine 125 particles implantation for multiple lung lesions. But, part of the lesions turned out to be primary lung NET at extensive stage, as the hilar and mediastinal lymphadenopathy. In addition, more lung lesions appeared in following CT scan several weeks later; and biopsy and pathological examination of lesions authenticated the diagnosis. The treatment strategy was changed immediately and chemotherapy and subsequent radiotherapy for lung NET was performed. Even so, the tumor progressed after a short remission period and the final prognosis was poor.

Delayed diagnosis at extensive stage may be one of the main reasons for poor prognosis, as in the other case the patient had already suffered pleural effusion when first diagnosed with small cell lung NET. As reported, about 30% of patients with SCLC were diagnosed at a limited stage. The survival for these patients has been improved by current treatment modality and the 5-year survival rate can be over 40% [29-31]. However, extensive stage SCLC has been generally considered incurable for the past 30 years and the median overall survivals in most studies is less than 11 months [32]. Therefore, a shorter interval of imaging recheck and an earlier diagnosis may be the only effective way to improve prognosis at present. In addition, bulky hilar and mediastinal lymph node involvement has been deemed to be a classic radiographic presentation of SCLC although the lesions in lung are often small or even unidentifiable, a feature that differentiates it from lung metastases. The use of PET scan can also increase the sensitivity for detection of lymph node involvement [22]. Closer attention to the imaging manifestation of hilar and mediastinal lymph nodes can help detect SCLC at an early stage. Ultimately, pathological evidence is necessary for the diagnosis and a series of typical pathological features and immunohistochemical manifestations of lung NET are available [33]. But it is still crucial to obtain prophetic and timely tissue information based on imaging findings for early diagnosis.

Treatment for de Novo Lung NET after LT

As discussed above, timely and early diagnosis is vital for the treatment of lung NET. Once diagnosed, therapies for lung NET, including surgery, chemotherapy and radiotherapy, should be given as soon as possible. However, more cautions should be taken when using these antitumor therapies in LT recipients. For operable de novo cancers, in order to qualify for surgery on these transplant recipients, the comorbidities need to achieve a survival greater than 50% over 5 years after the operation [34]. Because the risk of surgery for these patients, including infectious diseases and organ dysfunction is high, the benefit of surgery should outweigh the risks. Regarding the use of chemotherapy, the direct cytotoxic effects or interactions with immunosuppressive drugs can increase the risk of graft loss [34]. Additive or synergistic effects of chemotherapeutic medicine and immunosuppressive drugs can also lead to risk elevation of sepsis [34]. As for radiotherapy, no excessive toxic effect of standard doses of radical or adjuvant radiotherapy is observed in transplant recipients in previous research [1]. However, both concurrent and sequential radiotherapy may increase chemotherapy toxicity, including myelosuppression and organ function impairment, and more attention should be paid to adverse reaction management when chemoradiotherapy is performed.

Immunosuppression Modification

Although no current study has demonstrated the direct role of immunosuppression in the development of de novo lung NET in LT recipients, gradual minimization of immunosuppression should be the initial management for these patients. However, the lowest possible level of immunosuppression is not easy to reach in fact because accurate markers of insufficient immunosuppression are lacking. Furthermore, there were studies aiming to explore immunosuppression weaning protocols but the outcomes were unsatisfactory and the risk of rejection remained [35, 36]. Actually, complete withdrawal of immunosuppression can only be successful in a small proportion of LT recipients in the second year after transplantation [36]. In our study, immunosuppressive drugs in the second patient were unfortunately withdrawn during the first year after transplantation and rejection occurred several weeks later. Tapered dosage or even withdrawal of immunosuppression may likely retard the progression of lung malignancy in LT recipients, but early withdrawal of immunosuppression should be very careful. Further research on the accurate evaluation of excessive or insufficient immunosuppression may help find the best modification of the immunosuppression regimen.

CONCLUSION

Our research found that lung NET may have a higher proportional incidence of de novo lung carcinoma in LT recipients and should not be ignored when new on-set lung lesions occur in these patients. The prognosis may be even worse under chronic immunosuppression after LT. Early diagnosis is vital for the treatment of lung NET in LT recipients and prophetic and timely biopsy based on imaging findings is crucial for this early diagnosis.

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