

Letter to Editor

Cutaneous metastasis from pulmonary large cell neuroendocrine carcinoma in the scalp

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Introduction

Neuroendocrine tumor of the lung is classified into four subtypes according to the recent World Health Organization Classification: typical carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma (LCNEC) [1]. LCNEC is a relatively rare histopathological subtype of lung carcinoma, which accounts for approximately 3% of all lung carcinomas [1]. It has been well recognized that this type of carcinoma as well as small cell carcinoma of the lung show an aggressive clinical course [2].

The frequency of cutaneous metastasis from visceral malignancies is relatively rare. A recent analysis has shown that the overall incidence of cutaneous metastasis is 5.3% of all internal malignancies [3], and it has been estimated to occur in 0.7 to 9% of patients with internal cancers [4-8]. Hu et al. analyzed 124 cases of cutaneous metastases from internal malignancies [4]. They found that the rate of cutaneous metastases was 1.02%, and the most common primary site was the breast, followed by the lung, oral mucosa, colorectum, stomach, and esophagus [4]. In their series, 23 cases of lung carcinoma among 1,292 primary tumors (1.78%) showed cutaneous metastasis, and the most common histopathological subtype was adenocarcinoma (16/23 cases), followed by squamous cell carcinoma (5 cases) and small cell carcinoma (1 case), while no large cell carcinoma cases showing cutaneous metastasis were documented [4]. Only two cases of cutaneous metastasis of LCNEC (one

case was from the urinary bladder and the other was from the rectum) have been reported in the English-language literature [9, 10]. Herein, we report the first documented case of metastatic pulmonary LCNEC in the skin.

Case report

A 55-year-old Japanese male with a 40-year history of smoking (40 cigarettes /day) presented with persistent left chest pain at an outpatient clinic. Computed tomography revealed a tumorous lesion in the left upper lung. He was referred to our hospital for evaluation of the lung tumor. Laboratory examinations showed a mild elevated level of carcinoembryonic antigen (10.9 mg/mL (range < 5)), however, other tumor markers were within normal ranges (SCC1.0 ng/mL (< 1.5), proGRP 38.0 pg/mL (< 80.9), neuron specific enolase 8.8 mg/mL (< 16.3), and CYFRA 1.2 ng/mL (< 3.5)). A bronchoscopic examination failed to detect any carcinomas, and subsequently, lobectomy of the left upper lung with lymph node dissection was performed.

His post-operative course was uneventful, however, he presented with left lower back pain 3 months after the surgery. Computed tomography revealed a metastatic carcinoma in the left iliac bone, and then radiation therapy (total 30 Gy) was performed. Five months after the surgery, a nodular lesion was detected in the scalp. Physical examination revealed a relatively well-circumscribed subcutaneous nodule in the scalp. Biopsy of the nodule was performed. Computed tomography demonstrated multiple

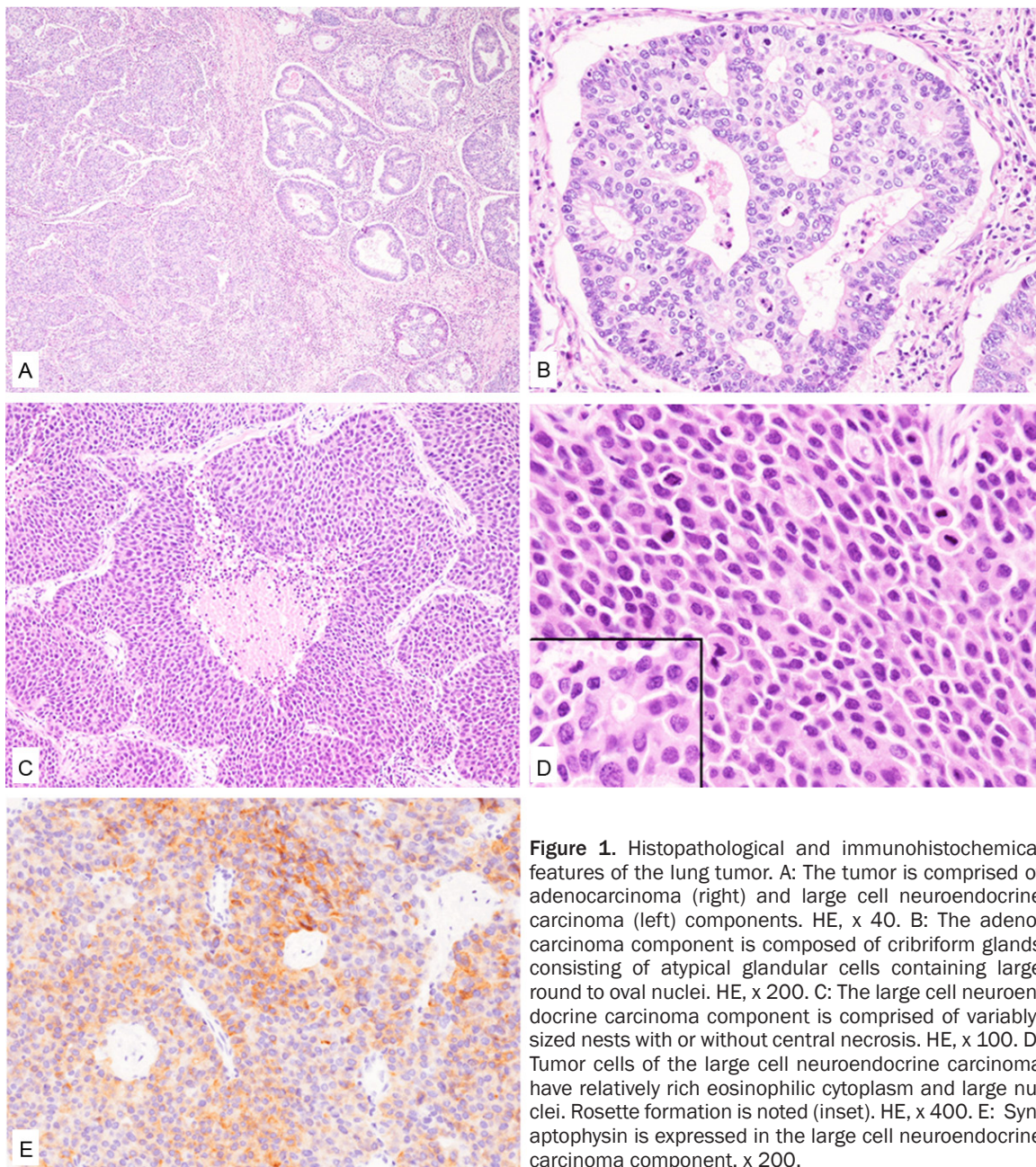


Figure 1. Histopathological and immunohistochemical features of the lung tumor. A: The tumor is comprised of adenocarcinoma (right) and large cell neuroendocrine carcinoma (left) components. HE, x 40. B: The adenocarcinoma component is composed of cribriform glands consisting of atypical glandular cells containing large round to oval nuclei. HE, x 200. C: The large cell neuroendocrine carcinoma component is comprised of variably-sized nests with or without central necrosis. HE, x 100. D: Tumor cells of the large cell neuroendocrine carcinoma have relatively rich eosinophilic cytoplasm and large nuclei. Rosette formation is noted (inset). HE, x 400. E: Synaptophysin is expressed in the large cell neuroendocrine carcinoma component. x 200.

metastatic lesions in the bilateral lungs and liver, and subsequently underwent chemotherapy (CDDP and CPT11).

Histopathological study of the resected lung specimen demonstrated two different carcinoma components within the lesion (**Figure 1A**). The major component, which accounted for approximately 60% of the tumor, was an adenocarcinoma (**Figure 1A and 1B**). This component was composed of cribriform or tubular glands, and the atypical glandular cells had large round

to oval nuclei containing small nucleoli (**Figure 1A and 1B**). No lepidic component was noted. Mitotic figures were frequently observed (48/10 high-power fields). The other component was composed of proliferation of variably-sized nests with or without central necrosis (**Figure 1A, 1C**). These neoplastic cells had relatively rich eosinophilic cytoplasm and large round to irregular-shaped nuclei (**Figure 1D**). Rosette formation was frequently observed (**Figure 1D, inset**). Mitotic figures were frequently noted (76/10 high-power fields). Both vascular and

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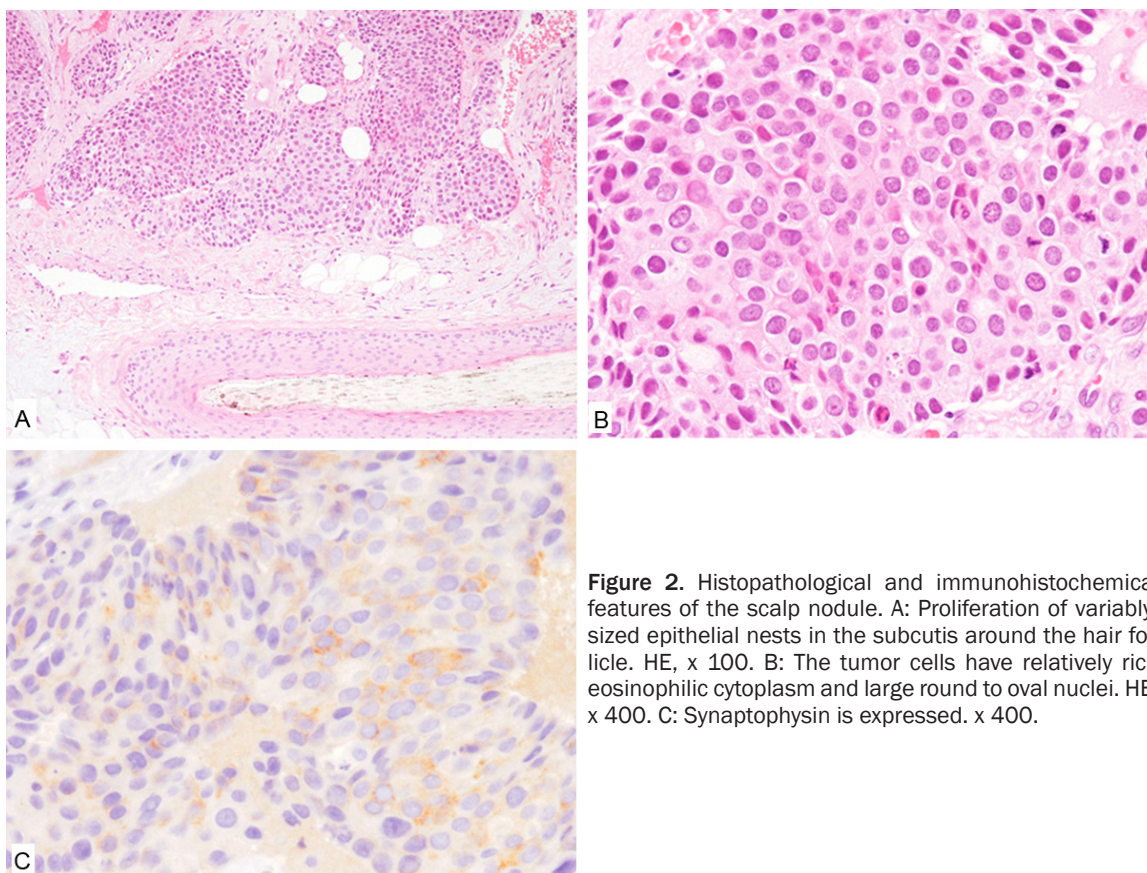


Figure 2. Histopathological and immunohistochemical features of the scalp nodule. A: Proliferation of variably-sized epithelial nests in the subcutis around the hair follicle. HE, x 100. B: The tumor cells have relatively rich eosinophilic cytoplasm and large round to oval nuclei. HE, x 400. C: Synaptophysin is expressed. x 400.

lymphatic invasions by the tumor cells were observed. This component was suspected as LCNEC. Pleural invasion was noted, however, no lymph node metastasis was present.

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [11-15]. Synaptophysin and CD56 were diffusely positive in the LCNEC component (**Figure 1E**), but negative in the adenocarcinoma component. A few chromogranin A-positive neoplastic cells were present in the LCNEC component, but absent in the adenocarcinoma component. TTF-1 was negative in both components.

Accordingly, an ultimate diagnosis of combined LCNEC (LCNEC and adenocarcinoma) (pT3N0M0) was made.

Histopathological study of the scalp nodule revealed proliferation of atypical epithelial cells that formed variably-sized nests in the subcutis (**Figure 2A**). The neoplastic cells had relatively rich eosinophilic cytoplasm and large round to oval nuclei (**Figure 2B**). Mitotic figures were fre-

quently seen (23/5 high-power fields). No adenocarcinoma component was present.

Immunohistochemical study revealed that these tumor cells were positive for synaptophysin and CD56 (**Figure 2C**), but negative for chromogranin-A and TTF-1.

Accordingly, an ultimate diagnosis of metastatic LCNEC of the lung in the scalp was made.

Discussion

In this report, we describe the first documented case of metastatic LCNEC of the lung in the skin. The lung carcinoma of the present case was combined LCNEC (LCNEC and adenocarcinoma), which is defined as a tumor that contains an LCNEC component and another non-small cell carcinoma component [1]. The incidence of combined LCNEC is very low. Ruffini et al. reported that only 0.43% of surgically resected primary lung carcinomas (5/1158 cases) were combined LCNEC (three of them had adenocarcinoma component, and the remaining two had squamous cell carcino-

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Table 1. Clinicopathological features of metastatic large cell neuroendocrine carcinoma in the skin

Case No.	Age/Gender	Primary organ	Metastatic site	Immunohistochemical characteristics	Reference
1	20/Male	Urinary bladder	Scalp	Synaptophysin (+), CD56 (+), TTF-1 (+)	[9]
2	58/Male	Rectum	Scalp	CD56 (+)	[10]
3	65/Male	Unknown	Head, neck, trunk, and leg	Synaptophysin (+), chromogranin A (+), CD56 (+), TTF-1 (-)	[18]
Present Case	55/Male	Lung	Scalp	Synaptophysin (+), chromogranin A (-), CD56 (+), TTF-1 (-)	

ma component), while the incidence of combined small cell carcinoma was 1.2% [16]. Recently, Yamada et al. analyzed the clinicopathological features of combined LCNEC, and they reported that the incidence of combined LCNEC was 0.6% of all surgically resected cases [17]. The most common carcinoma component that co-existed with LCNEC was adenocarcinoma (16/25 cases), followed by squamous cell carcinoma (8 cases) [17]. In the present case, metastatic skin lesion had only a LCNEC component. This may be due to the higher malignant potential of LCNEC than adenocarcinoma of the lung.

To best of our knowledge, only two cases of cutaneous metastasis of LCNEC have been reported [9, 10], although one case of LCNEC presenting with skin metastases of unknown origin has also been documented [18]. **Table 1** summarizes the clinicopathological features of these three cases of metastatic LCNEC in the skin as well as the present one [9, 10, 18]. All patients were male, and this condition mainly affected the middle-aged, however, a case of urinary bladder LCNEC occurring in a 20-year-old male has been documented [9]. The primary site was variable, including urinary bladder and rectum, and this is the first documented case of primary lung LCNEC metastasizing to the skin. The scalp was the most common site of metastasis (3/4 cases), and the remaining one case had multiple metastases in the head, neck, trunk, and leg [18]. All cases showed positive immunoreactivity for neuroendocrine markers. TTF-1, a transcription factor that is expressed in normal thyroid and lung tissues, was expressed in one case [9], but negative in two cases including the present one [18]. Approximately 50% of lung LCNEC demonstrates TTF-1 expression [17, 19, 20], and it has been recognized that LCNEC arising in non-pulmonary sites sometimes shows positive immunoreactivity for TTF-1 [20]. TTF-1 expression does not necessarily indicate lung origin in LCNEC cases, therefore, clinical history and surveillance of primary site is needed.

Metastatic LCNEC in the skin must be differentiated from Merkel cell carcinoma and primary LCNEC of the skin [9, 18, 21]. Merkel cell carcinoma is a rare primary cutaneous carcinoma. This type of tumor is thought to originate from (or differentiate toward) Merkel cells, which are mechanoreceptors present in the epidermis and skin appendages. The typical histopathological feature of Merkel cell carcinoma is proliferation of small round cells containing vesicular chromatin and inconspicuous nucleoli, however, Merkel cell carcinomas with large cell features have been reported [22]. Therefore, differentiation from Merkel cell carcinoma is necessary, and immunohistochemical analyses are usually useful. The characteristic immunohistochemical characteristics of Merkel cell carcinoma include dot-like expression of cytokeratin 20 (86.7%) and a lack of expression of TTF-1 (3.3%), although cases of cytokeratin 20-negative/TTF-1-positive Merkel cell carcinoma have been documented [23]. Recently, it has been documented that approximately 80% of cases of Merkel cell carcinoma harbor a novel polyomavirus, referred to as Merkel cell polyomavirus (MCPyV), and immunodetection with monoclonal antibody against MCPyV large T antigen has been recognized as a useful tool in the evaluation of Merkel cell carcinoma [24]. However, MCPyV-negative Merkel cell carcinoma does exist, and interestingly, MCPyV-negative Merkel cell carcinomas morphologically have more abundant cytoplasm and more irregularly shaped nuclei than MCPyV-positive cases [24]. Moreover, only a few cases of primary cutaneous LCNEC have been reported, which shows positive immunoreactivity for synaptophysin, and lacks chromogranin A and dot-like cytokeratin 20 expression [21]. Histopathological and immunohistochemical characteristics cannot differentiate primary cutaneous LCNEC from metastatic LCNEC. Therefore, a combination of clinical history, and analyses of histopathological and immunohistochemical features is needed for correct diagnosis.

Disclosure of conflict of interest

None.

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