

## Case Report

# Neuroendocrine carcinoma of the larynx with subcutaneous and intramuscular metastases: a case report

Song Hong<sup>1,3</sup>, Lin Li<sup>2</sup>, Xiwei Liu<sup>1</sup>, Chongqi Tu<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China; <sup>2</sup>Department of Pathology, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China; <sup>3</sup>Department of Orthopaedic Surgery, The Affiliated Hospital, Zunyi Medical College, 149 Dalian Road, Zunyi 563003, Guizhou, China

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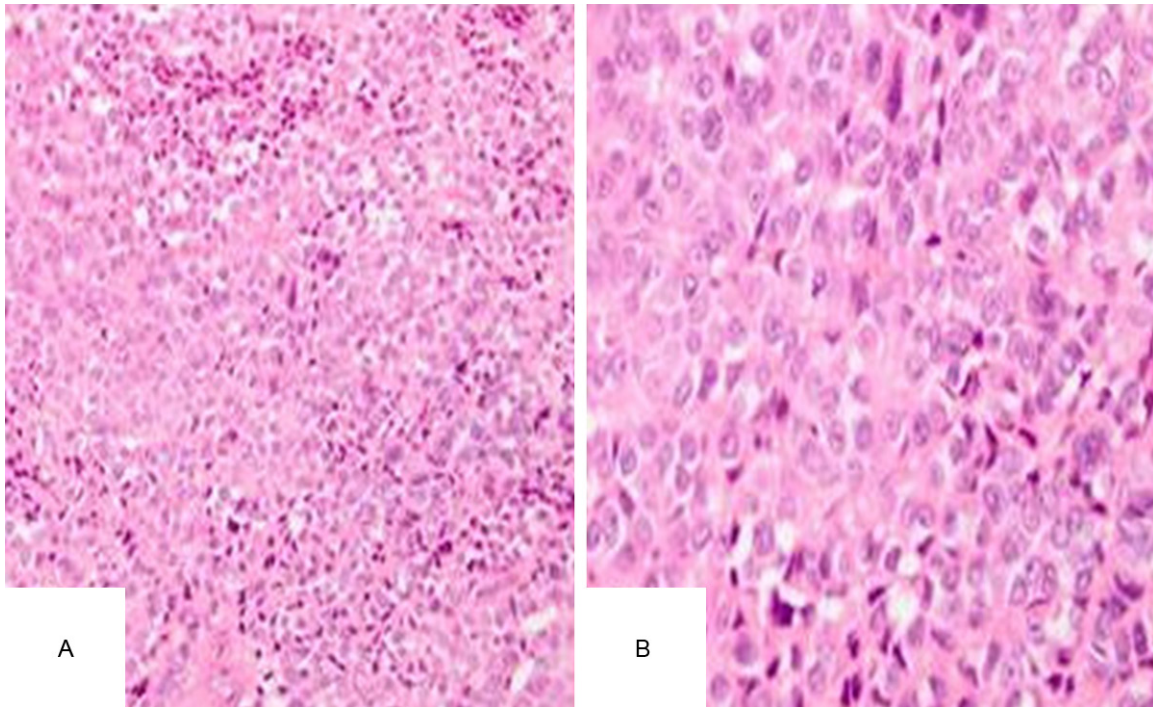
**Abstract:** Neuroendocrine carcinomas have become increasingly recognized as more reports are emerging to describe these rare tumors. Primary sites include the lung, liver, throat, and other organs. Laryngeal neuroendocrine carcinomas are relatively rare, and the subtypes as well as the prognoses are quite different in most cases. Metastases to the liver, lungs and other parts are common. However, metastases to subcutaneous tissues or muscles have been rarely reported. We report a case of a neuroendocrine carcinoma of the larynx with subcutaneous and muscle metastases.

**Keywords:** Laryngeal, neuroendocrine carcinoma, metastasis, subcutaneous, muscle

### Clinical findings

A 62-year-old Chinese male initially presented in December 2007 with a foreign body sensation in the throat area and coughed up white viscous phlegm. Subsequently, a localized mass was found in the left arytenoid. The patient's medical history was significant for hypertension, fatty liver and bilateral renal cysts, and a long-term smoking history. There were no other known environmental and family risk factors. He then underwent transoral endoscopic CO<sub>2</sub> laser surgery to remove this mass and a pathological diagnosis of poorly differentiated neuroendocrine carcinoma was found (**Figure 1**). The patient had adjuvant chemotherapy: five cycles of EP (VP-16 (Etoposide) 160 mg Days 1-3 + CDDP (cisplatin) 40 mg Days 1-3). He was followed by routine surveillance until August 2009 when a local recurrence of the laryngeal tumor was found on laryngoscopic biopsy. The patient underwent a total laryngectomy and bilateral cervical lymph nodes dissection. The pathological examination confirmed neuroendocrine carcinoma, with evidence of microscopic invasion of the nerves and lymph

nodes. The patient was again treated with adjuvant chemotherapy: five cycles of EP (VP-16 (Etoposide) 160 mg Days 1-3 + CDDP (cisplatin) 40 mg Days 1-3) and local radiotherapy to 50 Gy in 25 fractions. By June 2013, multiple subcutaneous and intramuscular masses were found that caused severe pain. They were distributed over the abdomen, the waist, the back, the shoulders, the thighs and the legs. The masses were not distinct on inspection. However, they were palpable, and the haphalgnesia was distinct and severe. Even the motion of the limbs was severely impaired; therefore, the patient required crutches. The masses were not clearly demarcated, and they were not mobile. Their texture was tenacious. MRI showed multiple subcutaneous and intramuscular lumps throughout the body. Laboratory data revealed an elevated enolase level to 16.3 ng/ml (normal value < 15 ng/ml). Ultrasound scans demonstrated masses that had low levels of echogenicity. Two masses were found in the muscle and the other masses were located in the subcutaneous tissue. The typical masses were seen on MRI (**Figure 2**). A CT scan of chest and abdomen did not show metastases to other



**Figure 1.** Microscopic photographs of primary neuroendocrine carcinoma (A: HE  $\times$  200, B: HE  $\times$  400). Tumor cells were arranged in trabecular shape, relatively consistent. Tumor cells were small with round or oval shape, with lightly red-stained cytoplasm.



**Figure 2.** MRI showed the subcutaneous and intramuscular lesions respectively, which were demonstrated by the pathological examination postoperatively.

internal organs. He underwent chemotherapy again, but the pain did not resolve before admission to the orthopedic department. The visual analogue scale (VAS) for pain was 9 before orthopedic surgery according to the VAS score system [1]. The resection of all the masses and the pathologic examination was performed by the orthopedic surgery team at West China Hospital. Pain was alleviated significantly postoperatively, and the VAS pain score de-

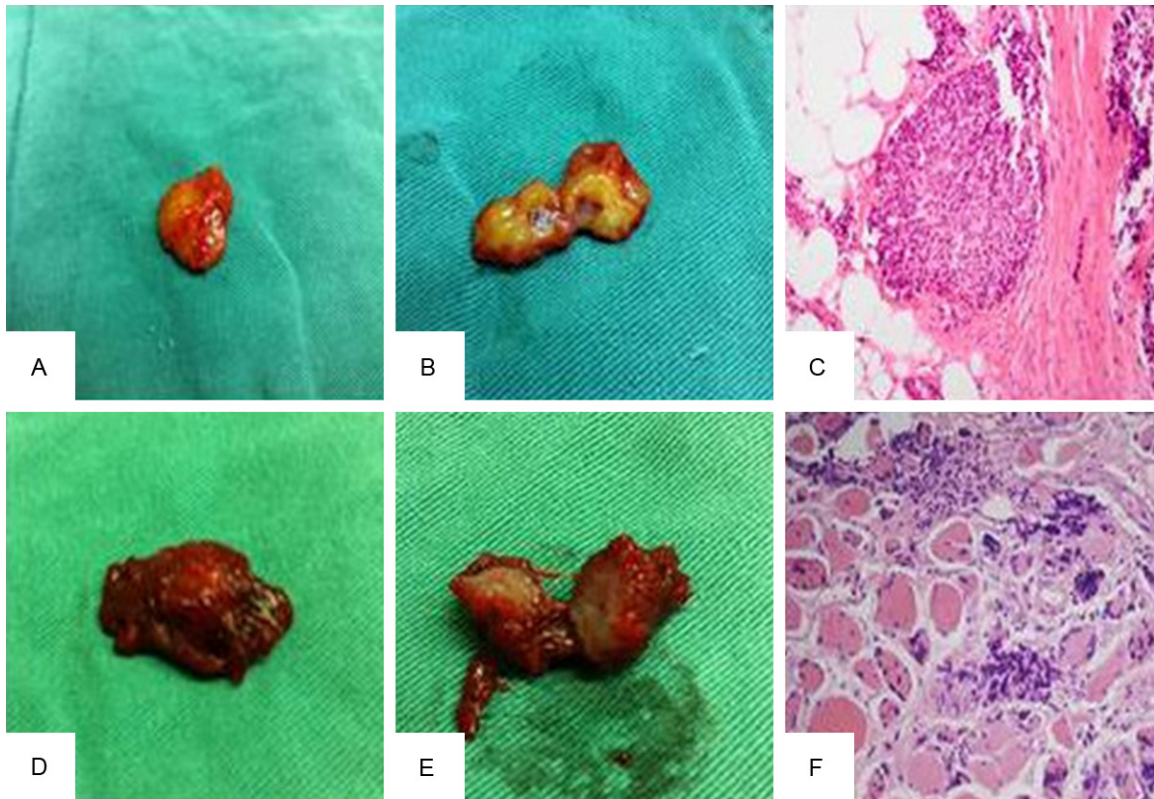
creased to 2. The subcutaneous and intramuscular masses were diagnosed as metastases of poorly differentiated neuroendocrine carcinoma of the larynx based on the histological study and immunohistological study. After surgery, a chemotherapy program (docetaxel 100 mg Day 1 + dacarbazine 300 mg Days 1-3 + calcium levofolinate 150 mg Day 1 + fluorouracil 750 mg Days 1-5) were performed for this patient for 6 cycles.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

#### Pathological findings

The pathological diagnosis of the primary laryngeal tumor was neuroendocrine carcinoma. The histopathological examination showed the metastatic tumor cells which were infiltrating the subcutaneous fat and connective tissue as well as the skeletal muscle (**Figure 3**). In addition, the tumor cells were arranged in nests or trabecula of variable sizes. The tumor was characterized by neuroendocrine carcinoma cells in mixed type, including one type of small-sized cells and medium-sized cells. The former dis-

## Atypical metastasis of neuroendocrine carcinoma



**Figure 3.** A. Subcutaneous lesion were embedded in the fat intraoperatively; B. The profile of the subcutaneous lesion showed the tumor located in the fat; C. Microscopic photographs demonstrated the subcutaneous lesion was metastatic neuroendocrine carcinoma (HE.  $\times 200$ ); D. Intramuscular lesion were embedded in the muscle fiber intraoperatively; E. The profile of the intramuscular lesion showed the tumor located in the muscle fiber; F. Microscopic photographs demonstrated the muscular lesion was metastatic neuroendocrine carcinoma (HE.  $\times 200$ ).

played a scant, eosinophilic cytoplasm with hyperchromatic nuclei, which were round or short spindle-shaped, and the nucleoli were not visible. The latter displayed a scant eosinophilic cytoplasm, and the nuclei were slightly staining, with an irregular round or oval shaped, finely granular chromatin pattern. In addition, the nucleoli were distinct and mitotic cells were visible but rare. The immunohistochemical profile of the tumor was characterized by strong and diffuse positivity for pan cytokeratin (PCK), chromogranin A (CgA), and synaptophysin (Syn). In addition, the tumor stained slightly positive for Ki67 (Figure 4).

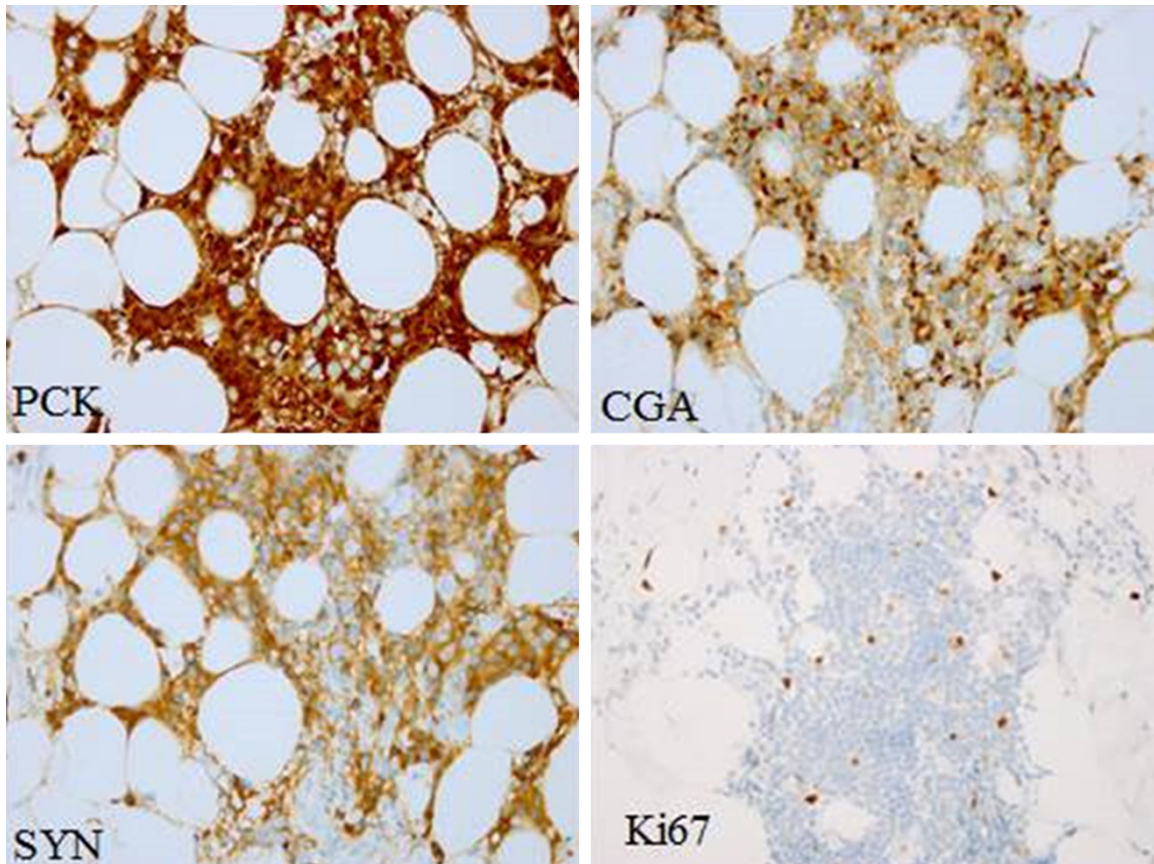
### Discussion

The present study reports a rare case of atypical metastatic laryngeal neuroendocrine carcinoma that was histologically diagnosed to be poorly differentiated tumor with metastatic lesions arising in the subcutaneous and muscular tissue. The most common primary sites of

the neuroendocrine carcinoma include the liver [2], lung [3], stomach [4], throat [5-8], skin [9], and even gingiva [6, 10]. Metastasis of neuroendocrine carcinomas to the skin has been previously reported [3, 11, 12], but reports about metastases to the subcutaneous tissue and muscle are rare.

After Goldman reported the first laryngeal neuroendocrine carcinoma in 1969, there have continuously been relevant reports. Laryngeal neuroendocrine carcinoma can be classified into the following categories based on the pathology [13]. The first category of tumors originates from epithelial cells and includes the following: (1) Typical carcinoid, which is low-grade malignancy that can be found in the gastrointestinal tract, larynx, lung, thymus, pancreas, testis, and so on. Tumor cells are medium-sized, and nuclei are located in the center and are round or eccentric with abundant cytoplasm, some of which are rather translucent, mitoses were rarely seen and heteromorphism is not obvious;

## Atypical metastasis of neuroendocrine carcinoma



**Figure 4.** Immunohistochemical staining of metastatic lesions showed positive for PCK, CgA, Syn and Ki67 (+) 2%, which conformed to the expression of metastatic poorly differentiated neuroendocrine carcinoma ( $\times 400$ ).

(2) Atypical carcinoid is seen in the lungs and may also occur in other organs. The tumor cells are morphological heterogeneous, and pleomorphic and mitotic cells are commonly seen. Tumor cells are arranged in nests, trabs, palisade, and central necrosis is common; and (3) Small cell neuroendocrine carcinoma, which is highly malignant tumor, commonly seen in the lung, but also visible in the esophagus, larynx, stomach, and other locations. Tumor cells are small, with a round or oval nucleus or oval, and the cytoplasm is sparse or shows a naked nucleus, mitotic figures are common, tumor cells diffuse and distribute into layers, and necrosis is common and fairly widespread. The second category of tumors originates from neural cells, which are believed to originate from the laryngeal paraganglioma, thereby forming the paraganglioma tumor [14]. Moreover, according to the differentiated degree [6, 15], this group of tumors can be further divided into the following subtypes: (1) Poorly differentiated neuroendocrine carcinoma; (2) moderately differentiated

neuroendocrine carcinoma; and (3) highly differentiated neuroendocrine carcinoma. We report a case of a small-sized poorly differentiated neuroendocrine carcinoma, which has the characteristics of small cell neuroendocrine carcinoma on morphology, immunohistochemistry CgA (+), Syn (+), and cytokeratin (+) (CK (+)). Metastatic tumors consisted of cells that infiltrated the subcutaneous fat and connective tissue and skeletal muscle widely. The tumor cells were arranged in nests or trabecula of varying sizes. Most of the cells were round and small with scant eosinophilic cytoplasm. Although mitotic cells were visible and rare, the nucleoli were distinct. Therefore, the tumor was diagnosed as metastatic poorly differentiated small-sized neuroendocrine carcinoma.

Laryngeal neuroendocrine carcinoma mainly occurs in older patients, most of whom have a long-term smoking history, and the initial symptoms are often throat discomfort and a hoarse voice. Laryngeal neuroendocrine carcinoma accounts for approximately 1% of laryngeal tu-

mors and different pathological types often have different prognoses. Of these, typical carcinoid and atypical carcinoid have a relatively good prognosis [14], and small cell neuroendocrine carcinoma has the worst prognosis. When the primary tumor is found, distant metastasis has often occurred, and metastases generally occur in bone, liver, lung, and brain [7, 8]. In our study, the laryngeal tumor recurred locally 2 years after the primary surgery, and the subcutaneous and muscular metastasis occurred 6 years later. The pathological diagnosis of metastatic subcutaneous and muscular tumor was consistent with the primary laryngeal neuroendocrine carcinoma. In addition, immunohistochemical results were partially positive for CgA, CK, Syn, and Ki67, thereby complying with the immunohistochemical expression of neuroendocrine carcinoma. Although the patient underwent chemotherapy and local radiation, the severe pain of the masses did not decrease. Therefore, morphine was used to relieve the pain. To determine the diagnosis and relieve the pain, the treatment plan often focuses on surgeries. After surgical resection, the postoperative pathological diagnosis was metastatic poorly differentiated neuroendocrine carcinoma, and immunohistochemical staining showed that the tumor cells were CK (+), CgA (+), Syn (+), and Ki67 (+) 2%, thereby conforming to the expression of metastatic poorly differentiated neuroendocrine carcinoma. The immunohistochemical study was significant for the diagnosis and type. Positivity for CK may be explained by the fact that the tumor arises from epithelial tissue. In addition, positivity for CgA and Syn was a sign for neuroendocrine carcinoma, thereby showing features of both neuroendocrine and epithelial differentiation. Ki67 reflected the reproductive activity of the tumor, the positive rate of which was 2% in this case, therefore suggesting the weak reproductive activity. In contrast, the tumor cells were not sensitive to chemotherapy.

The metastatic lesions were distributed widely and were diverse in size. The location of the lesions must be determined by palpation and ultrasound before general anesthesia is induced or otherwise some subcutaneous masses may be too small to be confirmed during the surgery. At the same time, the lesions must be widely resected because the margin of the tumor is not clear and invades the surrounding tissue. The postoperative VAS score was 2, and the symptoms were obviously relieved. The pa-

tient was still alive at the last follow-up after the operation, and no metastatic signs of other organs were found. Currently, there is no actual effective treatment for neuroendocrine small cell carcinoma of the larynx. The effect of surgery combined with chemotherapy and radiotherapy need further evaluation. Concurrently, the importance of studying the disease has to be stressed to find new breakthroughs in the diagnosis and treatment of it.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Chongqi Tu, Department of Orthopedics, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China. Fax: +86-28-85423438; E-mail: tcqbonetumor@163.com

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## Atypical metastasis of neuroendocrine carcinoma

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