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Large-cell neuroendocrine carcinoma (LCNEC) without pulmonary symptoms diagnosed in a cutaneous metastasis

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Statistical Analysis C
Data Interpretation D
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Patient: Female, 60
Final Diagnosis: Large-cell neuroendocrine carcinoma
Symptoms: Back pain
Medication: —
Clinical Procedure: Vertebroplasty
Specialty: Oncology

Objective: Unusual clinical course

Background: An atypical presentation of large-cell neuroendocrine carcinoma was diagnosed from a metastatic nodule on the chest wall.

Case Report: The patient was a 60-year-old female who presented with intractable back pain with an MRI showing an L3 compression fracture and multiple lesions in L3, L5, and the pelvis. The patient had a 40-pack-year smoking history. On admission, a small, non-tender nodule was noted under her left breast on the chest wall. CT and PET scan confirmed diffuse metastases in the lumbar spine, brain, lung, liver, and pancreas, without knowing the primary site. The patient underwent L3 vertebroplasty and removal of the nodule on the chest wall. The pathology report of the nodule showed large cell neuroendocrine carcinoma (LCNEC). Immunohistochemical stains were positive for cytokeratin AE 1/3, TTF-1, CD56, Synaptophysin, and chromogranin. The stains were negative for CK7, Napsin, cytokeratin 20, GATA-3, mammaglobin, and CEA. A pathology diagnosis of metastatic LCNEC was made, with the lung as the most likely original site.

Conclusions: Treatment consisted of pain control through an intra-thecal pump and whole brain radiation followed by systemic chemotherapy. This case elucidates the unusual cutaneous metastatic site for LCNECs, which was biopsied to confirm the diagnosis. This is the first case of LCNEC diagnosed by a cutaneous metastasis. In conclusion, it is possible to diagnose LCNEC of the lung at a distant metastatic site with careful histological and immunohistochemical examination, which can spare patients from more harmful biopsies.

MeSH Keywords: Neoplasm Metastasis • Carcinoma, Neuroendocrine

Abbreviations: **CD56** – cluster of differentiation 56; **CEA** – carcinoembryonic antigen; **CK7** – cytokeratin 7; **CK20** – cytokeratin 20; **CT** – computed tomography; **EGD** – esophagogastroduodenoscopy; **GATA-3** – GATA family of transcription factor-3; **LCNEC** – large cell neuroendocrine carcinoma; **MRI** – magnetic resonance imaging; **NCAM** – neural cell adhesion molecule; **NE** – neuroendocrine; **PET** – positron emission tomography; **TTF-1** – thyroid transcription factor-1

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Background

LCNEC is an aggressive and rare neoplasm and one of the most challenging diseases to diagnose and treat. It accounts for approximately 1.6–3.1% of all lung cancer [1]. LCNEC is now recognized as a histologically high-grade non-small cell carcinoma by WHO [2], categorized as a variant of large cell carcinoma. LCNEC has a distant metastasize rate of 65% [3] and poor prognosis even in early stages, with survival rates similar to small-cell lung carcinomas (SCCs) [4]. The life expectancy of stage IV LCNEC with distant metastasis was estimated at around 6 months [5]. Due to the fact that patients with LCNEC are less likely to present with pulmonary symptoms such as cough, hemoptysis, or postobstructive pneumonia [6], it poses challenges in early detection and diagnosis. The diagnosis of LCNEC is based on recognition of both neuroendocrine morphology (organoid pattern) and the immunohistochemical demonstration of specific neuroendocrine markers [2], such as chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM), also known as CD 56. To confirm the neuroendocrine origin in the tumor cells, at least 1 such marker must be positive.

In this paper we present an atypical case of LCNEC with widespread metastasized disease to the brain, liver, pancreas, and spine. The diagnosis was confirmed through the surgical resection of a cutaneous metastasis. This is the first case of LCNEC diagnosed by a cutaneous metastasis. It is possible to diagnose LCNEC of the lung at a distant metastatic site with careful histological and immunohistochemical examination, which can spare patients from more harmful biopsies.

Case Report

A 60-year-old white female presented with 4-week intractable back pain, which was not relieved by Dilaudid and Fentanyl prescribed by her primary care physician (PCP). She did not have leg weakness, or bowel or bladder incontinence. Pertinent social history includes a 40-pack-year history of tobacco smoking. She denied any pulmonary symptoms such as chest pain, cough, and hemoptysis. Initial physical exam showed severe tenderness and decreased range of motion of her back. A small non-tender nodule under her left breast on the chest wall was observed.

MRI of the lumbar spine before admission showed a marrow-replacing enhancing lesion in the left L5 pedicle, without an associated soft-tissue mass, a 1-cm enhanced lesion in the dorsal paramedian sacrum, and a compression fracture on L3. These findings were highly indicative of neoplastic metastases. After admission, a chest CT showed a focal thickening of the mid to distal esophagus (Figure 1A), and a

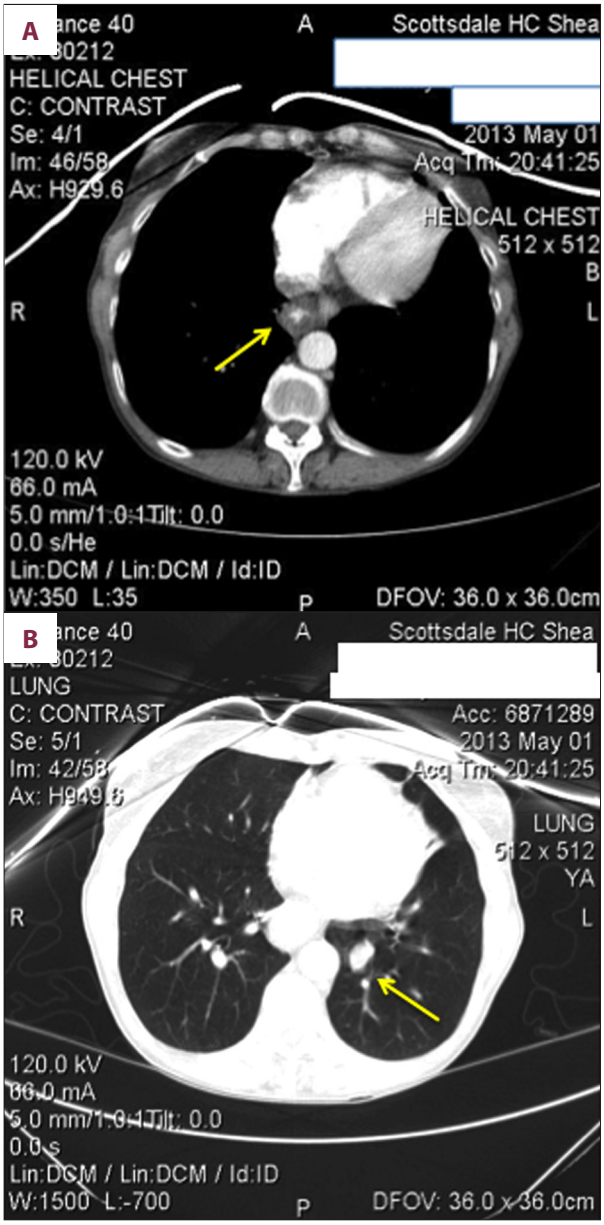

Figure 1. Radiographic study by chest CT scan. (**A**) CT showing a focal thickening of the mid to distal esophagus. (**B**) CT showing a new 1.7-cm loculated soft-tissue lesion in the left lower lobe.

new 1.7-cm loculated soft-tissue lesion in the left lower lobe (Figure 1B). The focal thickening of the esophagus justified an EGD with biopsy, which showed esophagitis and was negative for cancer.

PET showed disseminated metabolically active malignancy, and suspicious findings within the skeleton (Figure 2A, 2B), liver (Figure 2C), pancreatic head (Figure 2D), left pulmonary hilum, and left lower lobe. Brain MRI showed multiple intracranial masses compatible with metastatic disease (Figure 3).

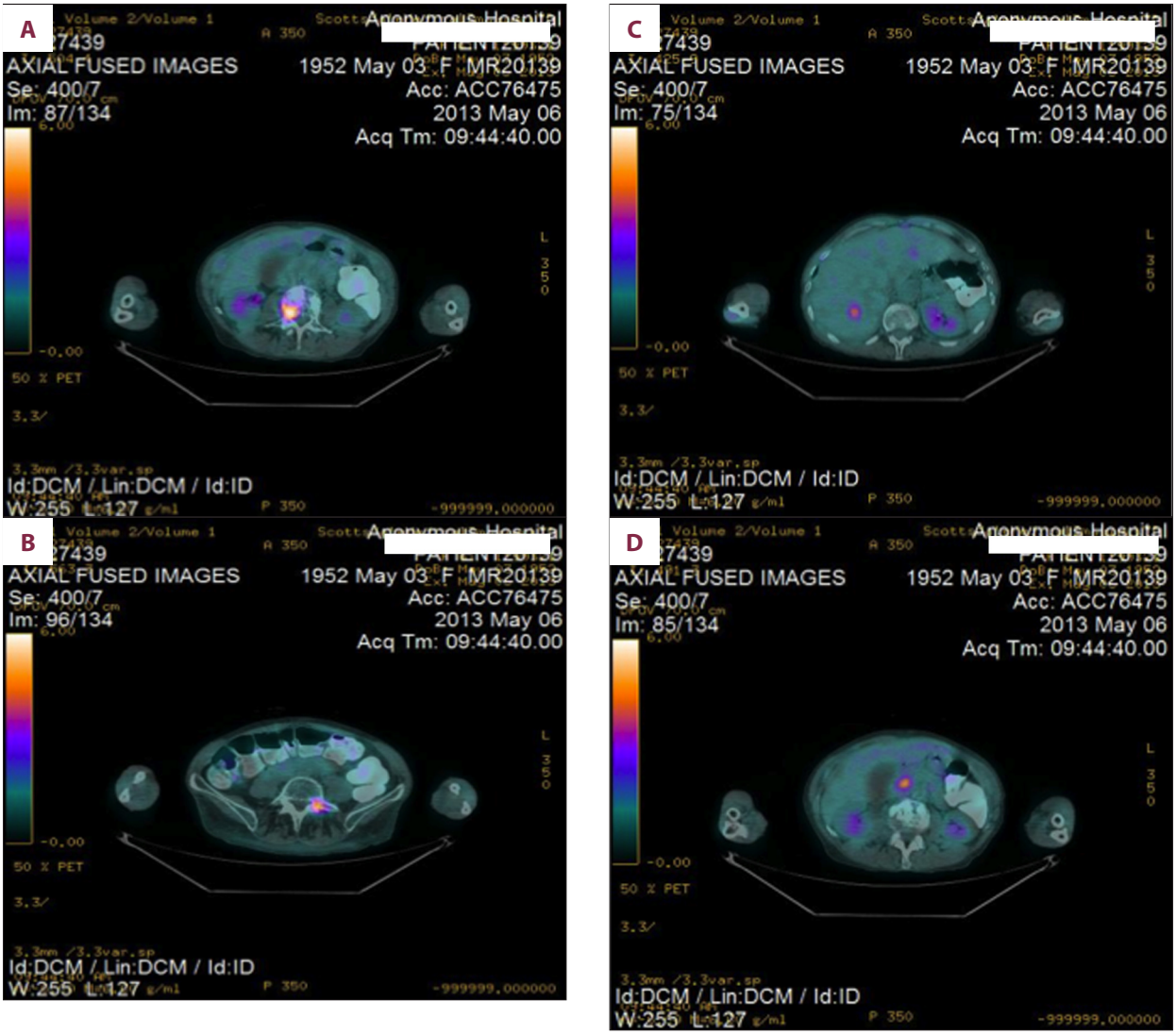

Figure 2. Radiographic study by PET scan. (**A**) Metabolically active lesion at right L3 pedicle and posterior vertebral body. (**B**) Metabolically active lesion at left L5 pedicle. (**C**) Metabolically active lesion within the liver. (**D**) Metabolically active lesion within the pacreatic head.

She underwent L3 vertebroplasty for the pain. In the same procedure, the nodule on the left chest wall was removed. The pathology report of the nodule confirmed LCNEC (Figure 4A). Immunohistochemical stains were positive for cytokeratin AE 1/3, Thyroid Transcription Factor 1 (TTF-1) (Figure 4B), CD56, Synaptophysin, and chromogranin (Figure 4C). They were negative for CK7, Napsin, cytokeratin 20, GATA-3, mammaglobin, and CEA.

Treatment consisted of pain control through an intra-thecal pump and whole brain radiation followed by systemic chemotherapy. Unfortunately, due to the advanced stage of her illness and aggressiveness of the tumor, her prognosis was very poor.

Discussion

Large-cell neuroendocrine carcinoma (LCNEC) is an aggressive neoplasm of the lungs, displaying immunohistochemical characteristics common to neuroendocrine tumors and morphologic features of large-cell carcinomas. The incidence of LCNEC is relatively low, being reported as 2.87% [7] or 3.1% [6]. LCNEC is determined by genetic risk factors such as epidermal growth factor receptor (EGFR) gene mutation[8] or tyrosine kinase domain (TKD) of the neurotrophic tyrosine receptor kinase (NTRK) gene [9]. Several reports indicate that 85% to 98% of patients who underwent surgical resection for LCNEC had a history of habitual cigarette smoking [6,10–12]. The mean age of onset ranges from 62 to 68 years, with a median of 65.8 years. Males are affected more frequently than

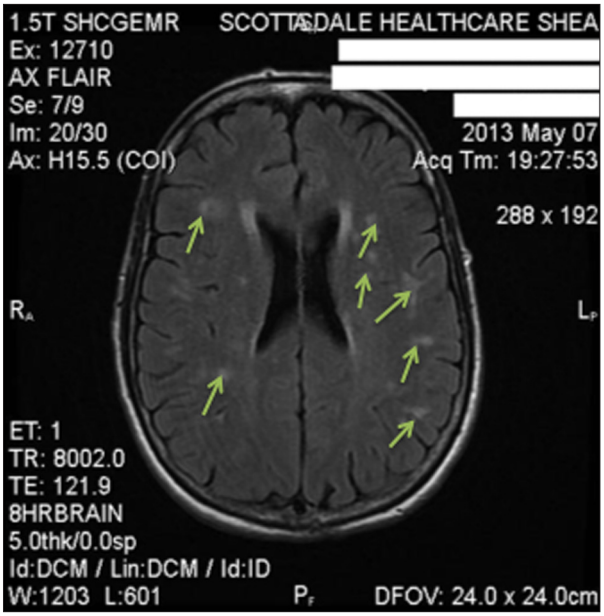

Figure 3. Brain MRI showing multiple intracranial masses compatible with metastatic disease.

females, ranging from 55% to 90% with a median of 85% for male preponderance [6,10–13].

This case demonstrated a patient who presented with diffuse metastasis upon radiological examination without any pulmonary symptoms. Typically, patients with LCNEC are less likely to present with pulmonary symptoms such as cough, hemoptysis, or post-obstructive pneumonia [6]. It has been reported that less than 20% of patients with LCNEC presented with cough or hemoptysis [14]. The remainder of patients presented with asymptomatic nodules, chest pain, or nonspecific flu-like symptoms. Paraneoplastic syndromes have not been frequently observed in patients with LCNEC [6,10,11]. LCNEC more frequently presents as a peripheral tumor as opposed to small-cell carcinoma, which are generally central in location [10].

Diagnosis of LCNEC is often difficult, which requires histological analysis, cytological evaluation, and immunohistochemistry. Morphologically, LCNEC tumors cells often show features of basaloid palisading, trabecular growth patterns, rosette formation, and organoid nesting [15]. The malignant cells are large with moderate to abundant eosinophilic cytoplasm, high N/C ratios, and numerous prominent nucleoli, easily distinguishing LNEC's cells from small-cell carcinoma [1]. Mitotic counts typically exceed 10 per 10 HPF of viable tumor [4]. All of these features are evident in the pathology report slides of this case.

In the presented case, the focal thickness of the esophagus prompted an EGD with biopsy, which was negative for malignancy. A new lesion was discovered in the left lower lobe in her lung, which may have needed biopsy if no other resources were

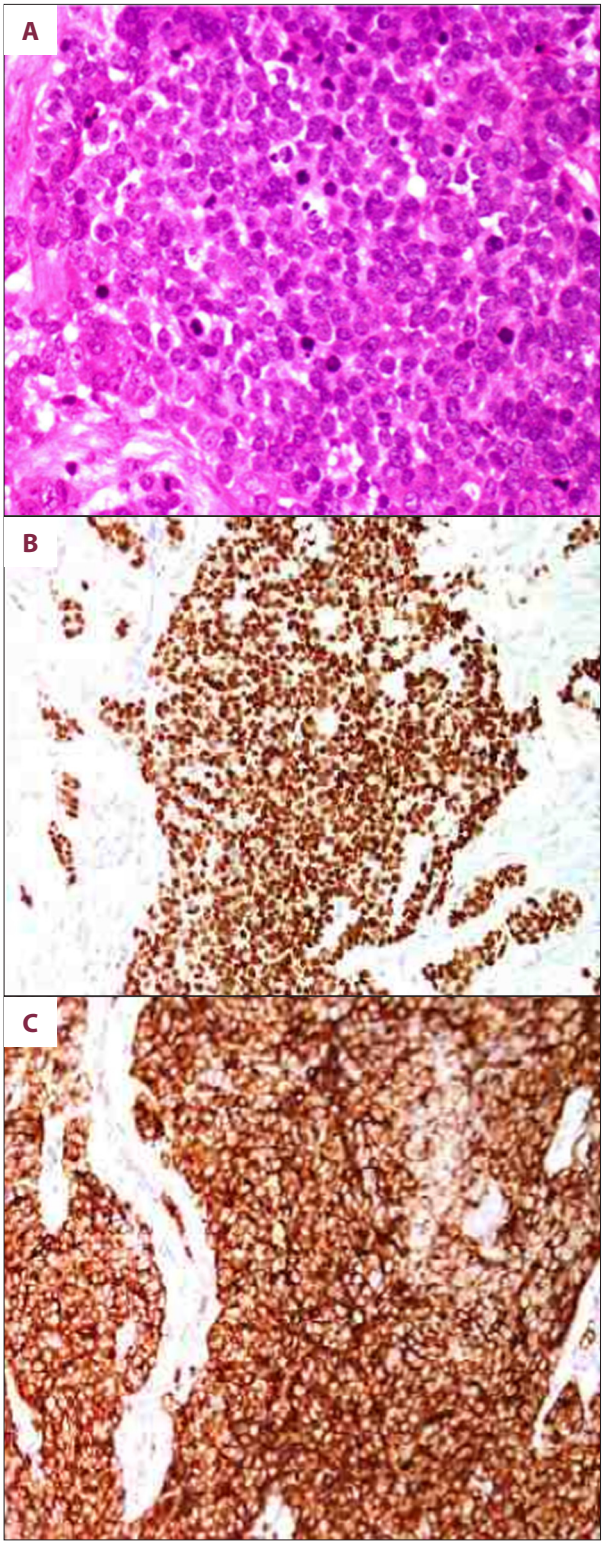

Figure 4. Immunohistochemical stains of the chest nodule. (**A**) >10 mitosis/2 mm^2 (10 hpf), cytologic features: large size, low N: C, nucleoli, coarse chromatin. (**B**) Positive immunostaining with TTF-1. (**C**) Positive immunostaining with chromogranin.

found. Instead, the nodule on her chest wall was removed and subsequently confirmed the diagnosis of LCNEC. As a result, she did not have to undergo the more hazardous lung biopsy. LCNEC has been reported with remote metastasis as the first presentation [5], but the current case is unique because the diagnosis of LCNEC of the lung was made by pathologic examinations of a single metastatic site without biopsy of the lung lesion.

The metastasis pattern and immunohistochemical markers indicated the pulmonary system as the most likely primary site of the tumor. The patient had extensive brain and bone metastasis with lesions in the left pulmonary hilum and left lower lobe, consistent with the manifestation of lung cancer [16]. Furthermore, positive TTF-1 (Thyroid Transcription Factor-1) and negative CK20 (Cytokeratin 20) stains strongly indicated that the primary site of the tumor was the pulmonary system [17]. TTF-1 is a nuclear transcription factor that regulates cell growth and differentiation in thyroid, lung, and selected brain tissue [18]. Cytokeratin (CK) 20 is a low molecular weight cytokeratin that is specifically expressed in the gastrointestinal tract and transitional cells of the urinary tract [19]. It was reported that TTF-1 had a specificity of 0.95 and a sensitivity of 0.69 for metastatic lung carcinoma, and CK20 had a specificity of 1.00 and a sensitivity of 0.69 for metastatic GIT carcinoma [19]. Therefore, these 2 proteins are ideal to be used to prove or exclude the lung and GIT origin, respectively, especially in patients presenting with metastatic carcinomas of unknown primary site. The presented case showed TTF-1 positivity and CK 20 negativity consistent with the pulmonary system as the most likely primary site of the tumor. However, the more harmful lung lesion biopsy was not performed.

The positive stain of 3 immunohistochemical markers (chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM)) confirmed the neuroendocrine origin [20]. Chromogranin A is a secretory protein involved in the biogenesis and storage of neurotransmitters and expressed by most neuroendocrine cells [21]. Synaptophysin is a synaptic vesicle glycoprotein in neuroendocrine cells and was regarded as one of the most specific markers of neuroendocrine differentiation [22]. NCAM, also known as CD56, is a cell-surface protein involved in cell-to-cell interactions during neural development and is the most sensitive and specific marker in confirming neuroendocrine differentiation in malignant neoplasms [22]. In the presented case, the conclusion is that the immunohistochemical pattern (Chromogranin+, Synaptophysin+, CD56+, TTF-1+, CK20–), along with the aforementioned morphological characteristics, are consistent with the diagnosis of a high-grade large-cell neuroendocrine carcinoma, having the pulmonary system as the most likely primary site.

LCNEC has similar prognosis and is treated with similar regimes as small-cell carcinoma [4,23,24]. The response rate of LCNEC to cisplatin-based chemotherapy was comparable to that of small-cell carcinoma [25,26]. Patients with LCNEC are more likely to develop recurrent lung cancer and have shorter survival time than patients with other types of non-small-cell lung cancer, even in those with stage 1 disease [27]. Most patients initially respond to chemotherapeutic agents, but early relapses and resistance to currently available treatments occur frequently [25]. The 5-year overall survival rate for resected LCNEC is approximately 35% and is significantly worse than the survival rate of 71.3% observed for large-cell cancer with no evidence of neuroendocrine morphology or differentiation [28]. Unfortunately, patients with stage IV LCNEC with distant metastasis have a much worse prognosis, with a 5-year reported survival rate of 0% [20]. The present patient was among this unfortunate group.

Conclusions

Large-cell neuroendocrine carcinoma (LCNEC) is a rare and aggressive neoplasm with a very poor prognosis. Chromogranin, Synaptophysin, and NCAM/CD56 are excellent histochemical markers to delineate tumors of neuroendocrine origin. TTF-1 and cytokeratin 20 further allow identification of the pulmonary system as the primary tumor location in such metastatic disease. The atypical presentation of LCNEC in the presented case was diagnosed from a metastatic nodule on the chest wall while doing vertebroplasty. We believe this is the first case of LCNEC diagnosed by a cutaneous metastasis.

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