Large Cell Neuroendocrine Carcinoma: Topic Review and a Unique Case of Metastasis to the Mandible

Keith M. Schneider · Alan Y. Martinez ·
Marcello Guglielmi

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Abstract There are few reports of large cell neuroendocrine carcinoma (LCNEC) metastasis to the head and neck region, and no cases reporting LCNEC from lung metastasizing to the mandible. LCNEC is not well reported in the literature due to recent changes in the criteria for diagnosis, revised in 2004 by the world health organization, due to its propensity for rapid growth and low 5 year prognosis. We present a 61 year old female diagnosed with LCNEC of the lung in October, 2007 treated with radiation and chemotherapy. Our patient had a PET scan performed in March, 2009 revealing no sign of metastasis. In July, 2009 she was seen for suspected sialadenitis by another department and referred to our oral and maxillofacial surgery clinic. Her signs and symptoms were consistent with metastatic disease to the mandible confirmed by histologic and immunohistochemical examination which revealed an invasive poorly differentiated non-small cell carcinoma. Palliative care was offered. Our patient died 2 years after initial diagnosis of lung cancer and 3 months after initial finding of metastatic disease. The rapid growth and spread of this cancer was surprising and knowledge of this cancer should be included in a differential diagnosis of expanding mandibular jaw lesions.

Keywords Neuroendocrine · Lung cancer · Metastasis · Oral cavity · Mandible

Introduction

Lung Cancer Overview

Cancer is the second leading cause of death in the United States, second to heart disease [1]. Lung cancer is the most common cause of cancer related death in men and women (29 and 26 %, respectively), responsible for 157, 300 deaths this year, with another 220, 520 of newly diagnosed cases. Although people of all ages are affected, peak incidence is with smoking adults between 55 and 65 years of age [2]. Tobacco use is the single most important risk factor for cancer and is responsible for 87 % of lung cancer deaths [3]. Prognosis of these patients correlates with the TMN staging system recently validated by the International Association for the Study of Lung Cancer (IASLC), and varies according to histologic subtype [4, 5]. The 5 year survival rate for metastatic lung disease is 3.5 %. Lung lesions arising from bronchial epithelium make up 95 % of lung tumors and are divided into 2 categories: small cell carcinoma, and non-small cell carcinomas (Table 1). Small cell carcinomas comprise 20 % of bronchogenic carcinoma, and are considered very aggressive and highly malignant. These cells exhibit morphologic and immunohistochemical characteristics similar to neuroendocrine cells, and are therefore also placed into a class of neuroendocrine lung carcinomas (NEC). There are three other types of lung NECs, and these fall under the class of non-small cell carcinomas of the lung. Non-small cell carcinomas are the most common and comprise the remaining 80 % of bronchogenic carcinomas. This class is further divided into 8 different subtypes, large cell carcinoma and carcinoid tumor subtypes exhibiting neuroendocrine characteristics. Classification of lung tumors is necessary for appropriate treatment.

K. M. Schneider (✉) · A. Y. Martinez · M. Guglielmi
Division of Oral and Maxillofacial Surgery, Department of
Surgery, MetroHealth Medical Center, 2500 MetroHealth Dr.,
Cleveland, OH 44109, USA
e-mail: kmsdental@sbcglobal.net

Table 1 Lung carcinoma nomenclature

Small cell lung carcinoma ^a
Non-small cell lung carcinoma
Squamous cell carcinoma
Adenocarcinoma
Large cell carcinoma
Large-cell neuroendocrine carcinoma*
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Carcinoid tumor
Typical carcinoid ^a
Atypical carcinoid ^a
Carcinomas of salivary-gland type
Unclassified carcinoma

^a Lung carcinomas exhibiting neuroendocrine morphology
Travis [41]

Neuroendocrine Lung Tumors

Neuroendocrine cells are those which produce a neurotransmitter, neuromodulator, or neuropeptide hormone. The hormone is released from a dense core of secretory granules via exocytosis in response to external stimuli. Pulmonary neuroendocrine cells are located within the epithelium lining the larynx, trachea, and bronchi down to the bronchiole-alveolar junction. As solitary cells or innervated clusters, these cells possess chemoreceptor activity, mechanosensory and nociception properties regulating the mechanisms responsible for alteration in bronchomotor and vascular tone [6–9]. Tumors of the lung with neuroendocrine morphology include a spectrum from low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to high-grade large-cell neuroendocrine carcinoma (LCNEC) and small-cell carcinoma (SCC) [10]. The criteria for diagnosing NECs were recently revised in 2004 by the world health organization (WHO) and are described in Table 2. Lung tumors with neuroendocrine differentiation share certain biochemical and morphologic characteristics. Primary neuroendocrine tumors are found throughout the body, like in the lungs and abdomen. They have also been found in parts of the head and neck region including the paranasal sinuses, sinonasal tract, nasopharynx, tonsils, soft and hard tissues within the oral cavity, tongue, the major and minor salivary glands, larynx, and esophagus [11–19].

Metastatic Cancer

As mentioned earlier, certain types of lung cancer present a risk of metastatic disease. Metastases are usually seen within intrathoracic lymph nodes, but distant metastasis to

the liver, bone, and CNS can occur. Metastatic tumors are more common in the 5th–7th decades of life, and most frequently originate from primary tumors in lung, breast, prostate, gastrointestinal tract, kidney, and thyroid. Metastatic carcinoma is the most common form of cancer involving bone. Spread to the jawbones is thought to originate by hematogenous spread, via the valveless paravertebral veins of Batson [20]. Tumor cells extravasate and implant into the posterior maxilla and mandible where abundant red marrow and rich vascular hematopoietic tissues are found [21, 22]. Metastatic jaw tumors represent 1–3 % of metastatic disease, and as high as 16 % based on autopsy study [23]. Hard tissues are more involved than soft tissues, 2:1, and occur in the mandible 80 % of the time. 25 % of metastatic jaw lesions represent the first sign of disease, while 23 % were found as the first indication of malignancy from a distant site [24].

Lesions usually present as smooth enlargement of the premolar/molar region, locally invasive and a rapidly progressive swelling common in post extraction sites. The involved portion of the mandible can be associated with pain and tenderness, and loosening of teeth. Numb chin syndrome, or mental neuropathy, is a sinister sign of metastatic disease. It has been described as an initial sign in multiple myeloma, lymphoma, and metastatic prostate, lung, and breast cancer. Numb chin syndrome may be a result of nerve compression or pathologic perineural invasion [25].

Diagnosis is based on clinical presentation, radiographic findings, and histologic review if biopsy is obtained. Radiographically, lesions may appear as a poorly defined radiolucency with some opaque foci and a “moth eaten” appearance. Findings may resemble periodontal disease, the PDL of associated teeth may be widened, or there may be no radiographic findings. Histopathology may be identical to the primary tumor or may be so different that it is unidentifiable.

A patient’s long term prognosis, site of pathologic origin, depth of invasion, degree of differentiation, and size of tumor must be considered before treatment. Treatment may range from biopsy to local excision, to chemotherapy, radiotherapy, and/or brachytherapy. Prognosis is largely predicted based on staging of disease, stage IV disease with a low survival past 1 year. The 5 year survival rate for metastatic lung disease is 3.5 % [2].

Case Report

Our patient was a 61 year old Caucasian female referred to our oral and maxillofacial surgery service in July, 2009 to rule out causes of left sided jaw pain and swelling. She reported a 5 week history of pain in the mandible

Table 2 Criteria for diagnosing neuroendocrine tumors

Tumor type	Criteria
Typical carcinoid	Carcinoid morphology and <2 mitoses per 2 mm^2 (10 HPF), lacking necrosis and $\geq 0.5\text{ cm}$
Atypical carcinoid	Carcinoid morphology with 2–10 mitoses per 2 mm^2 (10 HPF) or necrosis (often punctate)
Large-cell neuroendocrine carcinoma	A tumor with a neuroendocrine morphology (organoid nesting, palisading, rosettes, trabeculae) High mitotic rate: ≥ 11 per 2 mm^2 (10 HPF), median of 70 per 2 mm^2 (10 HPF) Necrosis (often large zones) Cytologic features of a non-small-cell lung carcinoma (NSCLC): large-cell size, low nuclear to cytoplasmic ratio, vesicular or fine chromatin, and/or frequent nucleoli. Some tumors have fine nuclear chromatin and lack nucleoli, but qualify as NSCLC because of large cell size and abundant cytoplasm. Positive immunohistochemical staining for one or more NE markers (other than neuron-specific enolase) and/or neuroendocrine granules by electron microscopy
Small-cell carcinoma	Small size (generally less than the diameter of three small resting lymphocytes) Scant cytoplasm Nuclei: finely granular nuclear chromatin, absent or faint nucleoli High mitotic rate: ≥ 11 per 2 mm^2 , median of 80 per 2 mm^2 Frequent necrosis often in large zones

HPF high power fields, NE neuroendocrine

Travis [41]

bilaterally with more recent onset left lower lip and chin paresthesia. She additionally reported changes in occlusion and difficulty chewing food. Her medical history was complex and included hypertension, peripheral vascular disease, carotid artery occlusion s/p left carotid endarterectomy, chronic obstructive pulmonary disease, diverticulosis of the colon, and LCNEC of the right lower lung lobe diagnosed in October, 2007. She was an 80 pack year smoker with no history of alcohol or drug use.

She was originally diagnosed with COPD by her primary care physician in April, 2007 due to history of chronic bronchitis. 5 months later the patient presented to the ED due to shortness of breath and tachycardia. CT protocol to rule out pulmonary embolism (PE) revealed a centrally located right lower lobe mass without evidence of PE (Fig. 1). Bronchoscopy with biopsy revealed a positive finding of LCNEC. The patient was referred to a multidisciplinary thoracic tumor board for management of lung cancer. Their course of management included radiotherapy with adjuvant chemotherapy without surgical resection. PET revealed central and peripheral hypermetabolic activity in the ipsilateral chest lymph nodes. She was staged as T2N1M0 based on staging guidelines for non-small cell lung cancer. She underwent 6,660 cgy in 37 fractions of radiation followed by 1 round of chemotherapy using carboplatin and paclitaxel in February and March, 2008. Her lung nodule was reduced and considered stable in June, 2008. Repeat imaging after 3 months was suspicious for recurrent lung tumor, but was negative for metastasis as confirmed by PET. Brachytherapy was performed to right lower lobe in November, 2008 using Iridium 192 with minimal benefit. In March, 2009, an interval

Fig. 1 Chest CT with contrast revealing centrally located lung tumor at time of initial diagnosis

increase in right infrahilar mass was confirmed via CT and PET, but still without sign of distant disease. Patient completed a second round of radiotherapy for a total of 30 fractions and was placed on Erlotinib in May, 2009.

In July, 2009, the patient was evaluated by another service for suspected sialoadenitis and treated with penicillin. She was referred to our service due to persistent bilateral mandibular pain and swelling. Extraoral exam revealed left mandibular body swelling that was tender to palpation, no apparent lymphadenopathy. Neurologically, she had intact cranial nerve (CN) VII, however she had left CN V mandibular division, inferior alveolar nerve paresthesia. Intraoral exam revealed slightly mobile tooth #18

associated with firm expansile mass palpated in buccal vestibule and floor of mouth. Panorex revealed radiolucency of left mandibular body with a “moth eaten” appearance. Lesion measured approximately 5 cm anteroposteriorly, 4 cm superoinferiorly extending from alveolar crest to inferior border, and periapical to teeth #'s 17, 18, 20, and 21 (Fig. 2). CT examination confirmed left mandibular jaw mass with cortical bone erosion, $5 \times 4 \times 3 \text{ cm}^3$ encompassing inferior alveolar nerve (Fig. 3). Incisional biopsy of lesion was performed and specimen reviewed by pathology department. Microscopic examination of the left mandibular bone and soft tissue showed invasive poorly differentiated non-small cell carcinoma consistent with LCNEC metastasis. The tumor cells from the original lung mass exhibited an organoid pattern of large polygonal malignant cells with a fibrous stroma and large hyperchromatic nuclei with prominent nucleoli and scattered mitotic figures (Fig. 4). The lesion in the mandible was somewhat better differentiated, with less necrosis than the primary lung tumor. However, tumors from both sites showed immunohistochemical staining for the neuroendocrine marker, synaptophysin.

Findings were communicated to thoracic surgery tumor board. Repeat PET scan confirmed the diagnosis of metastatic disease. In August, 2009 Teeth #'s 18 and 20 were extracted due to pain and periapical tissues were sent to pathology, further confirming LCNEC of mandible. CT chest further revealed LCNEC metastasis to liver. Palliative care was initiated after an additional round of radiation therapy was unsuccessful. The patient died October, 2009 in hospice care.

Discussion

LCNEC of the lung is an uncommon but aggressive neoplasm with a poor prognosis, and often associated with advanced disease at the time of diagnosis. Their overall incidence is from 1 to 3 % of all lung cancers, and

Fig. 2 Panorex revealing radiolucency of left mandibular body with a “moth eaten” appearance

Fig. 3 3D facial CT reconstruction revealing erosion of left mandibular body

Fig. 4 Mandibular lesion. **a** Organoid pattern composed of nests of large cell neuroendocrine carcinoma (Hematoxylin–eosin, original magnifications 100×). **b** Higher magnification shows polygonal cells with abundant cytoplasm, prominent nucleoli and occasional mitotic figures (Hematoxylin–eosin, original magnifications 400×)

approximately 40 % of resected neuroendocrine lung tumors [26]. There are four major types of neuroendocrine phenotypes in large-cell carcinomas based on NE morphology, immunohistochemical and electron microscopic findings. LCNEC occur in the seventh decade of life with an average age of 66, and occur in men 4:1 over women. 85–98 % of patients diagnosed with LCNEC have a history of smoking [26, 27].

The clinical presentation and natural history of LCNEC is similar to that of small cell lung carcinoma (SCLC). LCNEC are located typically in the lung periphery and upper lobes and less likely in the central region typical of carcinoid lung tumors [26, 28]. Because of their peripheral nature, patients' are less likely to present with mechanical symptoms. The tumor mass is circumscribed, with a necrotic tan-red cut surface on gross review [28]. Patients can be asymptomatic or present with chest pain, cough, hemoptysis, non-specific presentations including flu-like symptoms, dyspnea, and/or night sweats [29]. Paraneoplastic syndromes typical of other lung cancers are rare [30].

The term LCNEC refers to a group of pulmonary tumors that have a neuroendocrine phenotype by light microscopy, but do not meet the criteria for the three better recognized neuroendocrine tumors. Diagnosis is based on radiographic findings, clinical, and microscopic assessment. Routine chest X-ray, computer tomography (CT), and positron emission tomography (PET) are indicated and typically reveal a mass with average size 3–4 cm (range 0.9–12 cm). CT can also be used for percutaneous transthoracic guided needle biopsy. Sputum samples and biopsies are also obtained by bronchoscopy with or without biopsy, while mediastinoscopy, video-assisted thoracic surgery, and thoracotomy are other alternatives. Sputum samples can be evaluated for biochemical markers and by somatostatin receptor scintigraphy. Fine-needle aspiration specimens or thoracocentesis for patients with pleural effusions can be used to achieve diagnosis, but cytology specimens are often difficult to classify accurately. Microscopic assessment can establish morphologic features and aid in identification (Table 2). Immunoperoxidase staining using p63, CK5, CK6, neuroendocrine markers (chromogranin, synaptophysin and CD56) and TTF-1 are helpful [31]. Microscopic diagnosis is improved with immunohistochemistry. Synaptophysin is a glycoprotein that makes up part of the neuroendocrine secretory granule membrane and is recognized by monoclonal antibody (SY38) in a variety of neuroendocrine tumors [32]. When used in conjunction with morphology, it is useful in identifying neuroendocrine features of a tumor.

Treatment considerations include surgical resection, bronchoscopic treatments (i.e. Nd-YAG laser), chemotherapy, radiotherapy, and biotherapy (i.e. Interferon). Most LCNECs, as are SCLCs, are poor candidates for

surgical resection due to local/systemic spread. Some lung neoplasms with neuroendocrine morphology have also shown resistance to chemotherapeutic agents [33]. Patients with LCNEC are more likely to develop recurrent lung cancer and have shorter actual survival than patients with other types of non-small cell lung cancer, even in those with stage I disease [27]. Prognosis for patients diagnosed with LCNEC is poor with overall 5-year survival ranging from 13 to 57 % according to disease stage. Staging follows the TMN classification of malignant lung and bronchial tumors recently validated by the IASLC.

LCNEC is not well reported in the literature due to recent changes in the criteria for diagnosing NECs, revised in 2004 by the world health organization, due to its propensity for rapid growth and low 5 year prognosis. In a recent review of 5,000 resected lung cancers, 83 cases were found to be LCNEC (1.7 %) [26]. There are few reports of LCNEC metastasis to the head and neck region. As was the case with our patient, metastatic tumor spread to the oral cavity is often the first sign of distant disease [24]. Our patient had a negative PET scan for metastatic disease 3 months before the clinical finding of metastatic spread to the mandible. Hard tissues are involved more often than soft tissues 2:1, the posterior mandible and anterior attached gingival tissues most common [24, 34, 35]. Metastatic lung disease may be clinically unnoticed, may present with localized swelling that is tender to palpation, or may appear more severe with local necrosis of the tissues with or without purulent drainage.

There have been no reports specifically indicating LCNEC of the lung with metastasis to the mandible, likely secondary to the recent WHO guidelines. A very comprehensive review published by Hirshberg reported a total of 673 cases of metastatic oral tumors from years 1916 to 2006. Of these, 16.6 % (112 cases) were from lung origin, 8.6 % (58 cases) found in the jawbone, with a male predilection. Lung cancer phenotype was not emphasized in the study. These results correlate well with smaller studies reported in the literature [36, 37]. Bodner specifically reported 2 cases of non small cell carcinoma of the lung [38]. One patient was a 67 year old female with an exophytic mass associated with the mandibular body, and the second patient was a 71 year old male with a periapical lesion associated with the anterior mandible. Sugiura reported a patient with LCNEC of the lung with metastases to the tonsil in a 66 year old female [39]. This patient, like ours, had a pathologic course complicated with recurrence and metastatic disease to the liver. Liver metastasis is relatively uncommon, and found in only 2 % of patients with lung carcinoma [9]. Her original lung mass was in the periphery unlike our patient who had a central lying lesion. Both our patient and the patient reported by Sugiura died within 3 months of metastasis to the head and neck.

The oral and maxillofacial surgeon is met with an ethical dilemma when treating the terminally ill patient. We must balance our patient's well being while trying to manage their pathologic condition. A decision needs to be made with the patient regarding definitive treatment versus palliative care. Our patient underwent a 3 month transformation that led to her demise. We opted for palliative treatment in this case based on her clinical complaints of difficulty chewing on the mobile teeth. If our patient had desired complete resection with reconstruction of the mandibular lesion, we would need to ask ourselves if placing the patient in a state of long term recovery is in her best interest given the dismal short term prognosis associated with such lesions. Our patients need to be educated thoroughly before embarking on treatment.

Conclusion

LCNEC is generally associated with an overall poor prognosis with a median survival of 17 months [40]. The rapid growth and spread of this cancer was surprising and knowledge of this cancer should be included in a differential diagnosis of expanding mandibular jaw lesions, particularly when patients have known lung cancer of neuroendocrine morphology.

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