Med Oncol (2012) 29:1405–1408
DOI 10.1007/s12032-011-9996-7

CASE REPORT

Extrapulmonary small cell: a novel case of small cell carcinoma of the thyroid gland

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Received: 16 May 2011 / Accepted: 18 May 2011 / Published online: 5 June 2011

Abstract Neuroendocrine tumors comprise a large group of malignancies which share unique morphological features and are characterized by the presence of neuroendocrine markers such as synaptophysin, chromogranin-A, and CD56 (N-CAM), ranging from indolent tumors, such as carcinoid tumors, to aggressive tumors, such as small cell carcinoma. The lung is the most common site for primary neuroendocrine tumors. Extrapulmonary primary sites of small cell carcinoma are rare but have been documented arising from various sites including esophagus, stomach, colon and rectum, gallbladder, thymus, salivary gland, ovary, cervix, bladder, prostate, and skin. We present a case of small cell carcinoma arising from the thyroid gland, a site not previously described in the literature. A 59-year-old woman presented with a thyroid mass, which, after resection, showed small cell morphology and positive immunostains for TTF-1, synaptophysin, chromogranin-A, CD56, etc. Five months after diagnosis, she had widely metastatic disease. After a near-complete response to the first chemo-treatment, her disease progressed. Following local radiation and more rounds of chemotherapy, she succumbed to the disease, 15 months after diagnosis. Our patient had no pulmonary lesions at the time of diagnosis to suggest metastasis from the lung. Much like its pulmonary counterparts, this small cell carcinoma of primary thyroid origin displayed an aggressive clinical course and poor outcome. Although it shows early sensitivity to chemotherapy, small cell carcinoma remains a difficult-to-treat cancer with a poor prognosis and can rarely be seen originating in organs outside of the lung.

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Keywords Extrapulmonary · Small cell carcinoma · Thyroid gland · Neuroendocrine · Prognosis

Introduction

Neuroendocrine tumors comprise a large group of malignancies which share unique morphological features and are characterized by the presence of neuroendocrine markers such as synaptophysin, chromogranin-A, and CD56 (N-CAM) [1]. They make up a histologically diffuse group of cancers which include pheochromocytoma, Merkel cell carcinoma, pancreatic islet cell tumors, carcinoid tumors, neuroblastoma, and medullary carcinoma of the thyroid.

The lung is the most common site for a primary neuroendocrine tumor. This collection of tumors range from well-differentiated neuroendocrine tumors, such as carcinoids and atypical carcinoids, to poorly differentiated tumors, such as small cell and large cell neuroendocrine carcinomas. Small cell carcinomas, also referred to as oat cell or anaplastic cell carcinomas, make up approximately 20% of all primary lung carcinomas. As a whole, small cell carcinomas are very aggressive neuroendocrine tumors with high mitotic indices that are usually widely metastatic on diagnosis. Histologically, small cell carcinoma can be distinguished from other cell types by their small-sized cells with ill-defined borders that are round-to-oval in shape and typically arranged in clusters or trabeculae. The cells often characteristically show "molding of the nuclei" in which the nuclei conform to each others contours. They also tend to have sparse cytoplasm and nuclei with finely dispersed, granular chromatin in a so-called salt-and-pepper pattern [1, 2]. Typically, the high cellular turnover can be evidenced by findings of necrosis seen as the cells outgrow their blood supply.

Extrapulmonary primary sites of small cell carcinoma are rare but have been documented arising from various sites including esophagus, stomach, colon and rectum, gallbladder, thymus, salivary gland, ovary, cervix, bladder, prostate, and skin [3, 4]. According to the NCCN, the most common extrapulmonary sites of origin, in order of decreasing frequency, are the cervix, esophagus, larynx and pharynx, colon/rectum, and prostate [5]. One extrapulmonary site of origin that has not been well described in the literature is the thyroid gland. Here, we present a novel case of small cell carcinoma arising from the thyroid gland and describe its clinical course.

Case presentation

In February 2009, a then 59-year-old woman palpated a nodule in her thyroid that she noticed after a routine root canal procedure. Within a few weeks, she felt a lymph node in the left side of her neck and began to experience swallowing difficulties. Otherwise, she had no complaints and was in good overall health. She denied any pain, fevers, or weight loss. Her past medical history was significant only for hypertension and lipomas of her right breast and left flank. She had been a smoker in the past, but quit 27 years prior to diagnosis, and only rarely drank alcohol. Her family history was significant for an unknown type of lung cancer in her father and a sister diagnosed with breast cancer at age 50.

In April 2009, she underwent a fine-needle aspiration of the thyroid nodule, which confirmed the presence of a poorly differentiated carcinoma. A staging PET-CT showed hypermetabolic uptake in the left lobe of the thyroid and in the cervical soft tissue. Within a few weeks, she underwent a total thyroidectomy with neck dissection. The pathology revealed a high-grade neuroendocrine carcinoma of small cell type with extensive necrosis and foci of squamous differentiation involving both thyroid lobes and extending into the parathyroid glands. The surgical margins, as well as 11 of 15 lymph nodes, were also positive for carcinoma. There were numerous foci of lymphovascular invasion as well as 5 peri-thyroidal tumor nodules, which may have suggested the possibility of complete replacement of other lymph nodes by tumor. Additionally, there were small foci of papillary carcinoma identified on the left measuring 3.5 mm and on the right two foci 1.5×1.0 mm.

Immunohistochemical stains were positive for CD56, neuron-specific enolase, synaptophysin, TTF-1, Cam5.2, CEA, Bcl2, and P53 and were focally positive for chromogranin. In addition, the tumor was focally positive for P63 and CK-903 in foci of squamous differentiation. It was negative for vimentin, calcitonin, CD45, pan-cytokeratin, and S100. A Ki-67 immunohistochemical stain showed a very high proliferation index, consistent with small cell carcinoma.

She presented to our office for further evaluation and management one month after her surgery. Her only complaints at that time were of mild pain at the surgical site, mild constipation, and lower back pain. On physical examination revealed a well-nourished, well-developed woman of 154lbs. The surgical site was well healed with some mild induration of the skin. No masses or lymphadenopathy were detected, and the remainder of the examination was unremarkable. Because of chronic back pain, we obtained an MRI L-spine, which confirmed numerous osseous lesions consistent with metastatic disease from L2-S1. Approximately 6 weeks after the surgery, a repeat PET-CT demonstrated a large, recurrent left thyroid mass, with an SUV of 8.2, as well as new hypermetabolic hepatic lesions and diffuse bony lesions in the spine, pelvis, and left femur.

Because of her diffusely metastatic disease, she was treated with chemotherapy in accordance with NCCN guidelines for poorly differentiated neuroendocrine tumors. In July, she began inpatient chemotherapy treatments with cisplatin and etoposide, which continued for six cycles. She had an excellent response to the treatment, as evidenced by a repeat PET-CT in September, which did not reveal any evidence of metastatic disease. Her last chemotherapy of this regimen was completed in October 2009, approximately 8 months after her initial diagnosis. The regimen was tolerated well with only marginal symptoms including mild sore throat, intermittent pain at the surgical site, and fatigue.

Physical examination at that time revealed mildly elevated blood pressure (150/80 mmHg), chemo-induced alopecia, focal tenderness around the horizontal surgical scar in her neck, and soft, tender bilateral submandibular lymph nodes. She had a near-complete response as evidenced by another PET/CT, in November 2009, which showed only a low-grade, metabolically active focus within the left post-thyroidectomy bed with a soft tissue nodule measuring 1.6 cm. Metabolic uptake seen in previous studies, including the diffuse osseous metastases, was not seen at this time.

However, because of her persistent neck pain as well as the hypermetabolic PET-CT findings at the thyroid bed, she was given a course of radiation, which finished at the end of December. Following the local radiation, she continued to suffer from progressively worsening pain in her throat secondary to enlarging lymph nodes, as well as continued fatigue and weight loss. She also had signs of disease progression when CT scans revealed a new metastatic focus in the right upper lobe of the lung.

Due to the local and systemic recurrences, she was given second-line chemotherapy with topotecan. Again, the

therapy managed to palliate her pain and dysphagia; however, the CT imaging showed progressive disease. After only 2 cycles, approximately 7 weeks later, worsening cervical and supraclavicular lymphadenopathy as well as new hepatic lesions, ranging in size from less than 1 to 4 cm in greatest diameter, was seen. In addition, new osteolytic and blastic metastatic lesions and a possible metastatic focus in the spleen were documented, all reflecting a rapidly growing tumor burden.

At that point, her chemotherapy regimen was changed to paclitaxel and carboplatin every three weeks. Once again, the new regimen provided symptomatic improvement of her neck pain and dysphagia; however, her disease continued to progress. Her level of fatigue, appetite, and overall performance status continued to decline. She eventually succumbed to the disease in June 2010, approximately 15 months after her diagnosis.

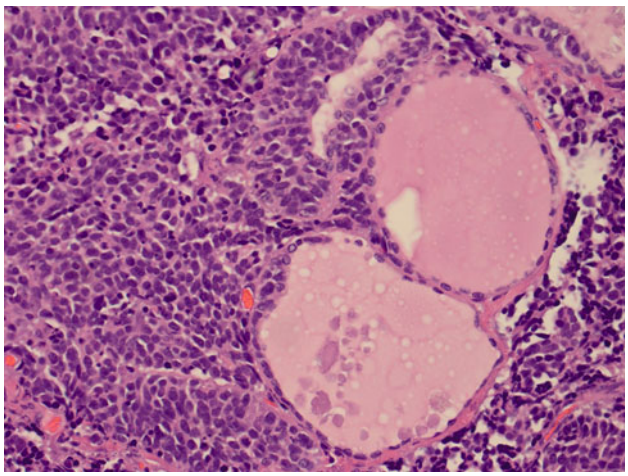

Fig. 1 Small cell carcinoma adjacent to thyroid follicles, H&E staining at low power

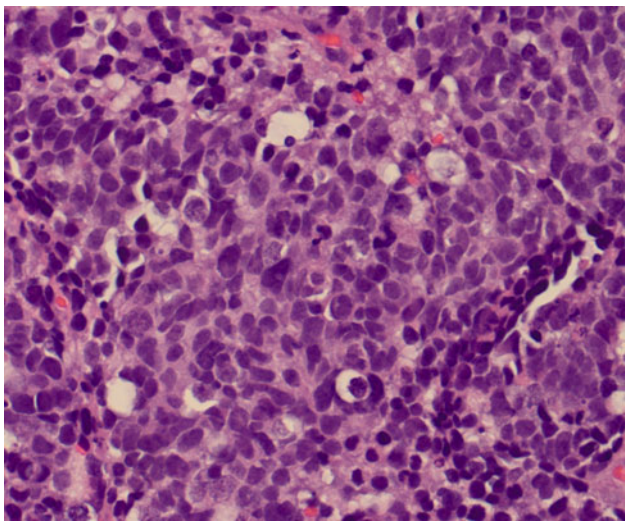

Fig. 2 Small cell carcinoma adjacent to thyroid follicles, H&E staining at high power

Discussion

Our case represents a unique presentation of small cell cancer of the thyroid that has not been well reported in the literature. Traditionally, nomenclature for the designation of small cell carcinoma has been somewhat controversial. The diagnosis is made based on distinct morphologic features along with characteristic cell markers for neuroendocrine tumors. Some [6, 7] have tried to further subclassify the different small cell carcinoma types into categories such as oat cell type, pure intermediate cell type, small cell/large cell type, etc. At this time, this division has not proved to be clinically useful due to the fact that all of the subtypes have a similar clinical course and prognosis. Reviews of limited disease extrapulmonary small cell carcinoma, in sites other than cervix, estimate an overall survival of 9.6 months [3].

Similar to medullary thyroid cancer, the pathology from our patient was neuroendocrine-derived as evidenced by positive markers for CD56, synaptophysin and chromogranin. Figures 1 and 2 are H&E stains from our patient's pathology at low and high power, respectively. The "molding of the nuclei" can be seen in these images. Figure 3 shows that the specimen is positive for CD56, and Fig. 4 demonstrates positivity for synaptophysin immunostaining. The histology is poorly differentiated with a substantial amount of necrosis, a prominent feature of small cell carcinoma. These findings are often seen in cases of small cell lung cancer and would be atypical for medullary carcinoma. Also consistent is the high proliferation index, as evidenced by the greater than 90% positivity for Ki-67 seen in Fig. 5. The tissue also stained negative for calcitonin, which is present in the vast majority of medullary thyroid cancer.

Because the pathology from our patient was also significant for foci of papillary carcinoma as well as squamous differentiation, one could argue that the poorly differentiated cancer from our patient may have evolved from one of these cell types. However, these foci made up less than 4% of the entire specimen, and the majority of the gland was replaced by the small cell morphology. Therefore, given all these factors, combined with lack of evidence of other systemic disease on diagnosis, we were confident that this case represented true small cell carcinoma of thyroid origin. Our patient's tumor was positive for TTF-1, which may suggest a lung origin; however, the original scans failed to show any pulmonary lesions. In fact, pulmonary metastases were not seen in our patient until 11 months after the original diagnosis, which was again consistent

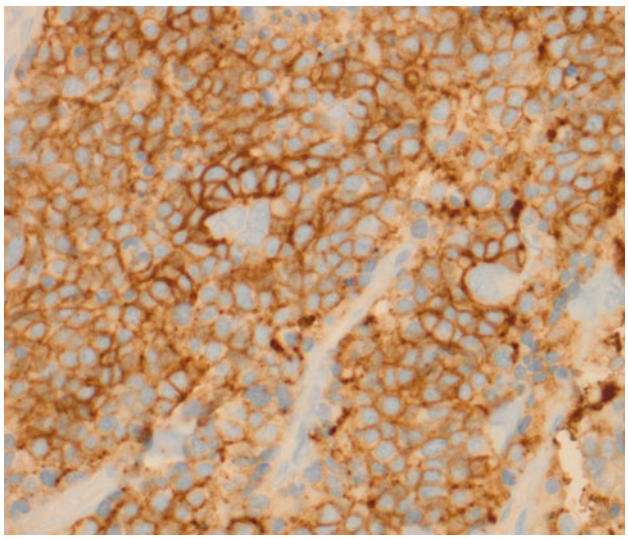

Fig. 3 Small cell carcinoma, cd56 immunohistochemical staining

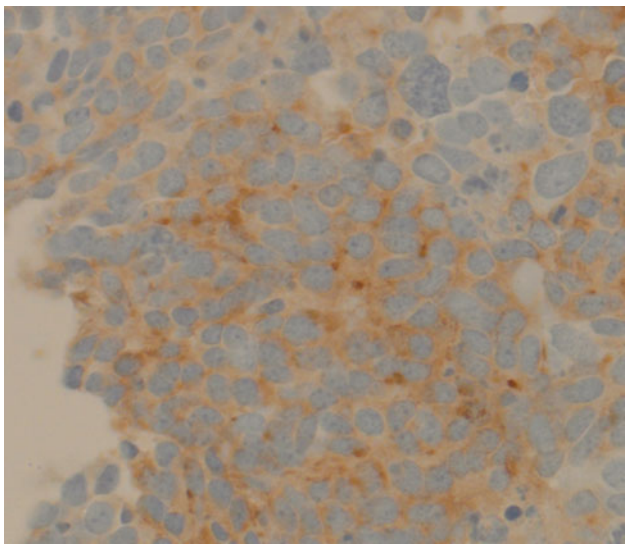

Fig. 4 Small cell carcinoma, synaptophysin immunohistochemical staining

with a true thyroid origin. The pathology samples were also reviewed by an outside pathologist who agreed with our diagnosis.

Our patient was treated with chemotherapeutic regimens that are effective in small cell cancer of the lung and initially had an excellent response to therapy. However, the near-complete response to chemotherapy did not last long. The various chemotherapeutic agents may have slowed the growth of the cancer, but as with most small cell carcinomas of lung origin, the results were short-lived. The natural history of this case is consistent with the aggressive and highly metastatic course seen in the small cell lung cancer patients.

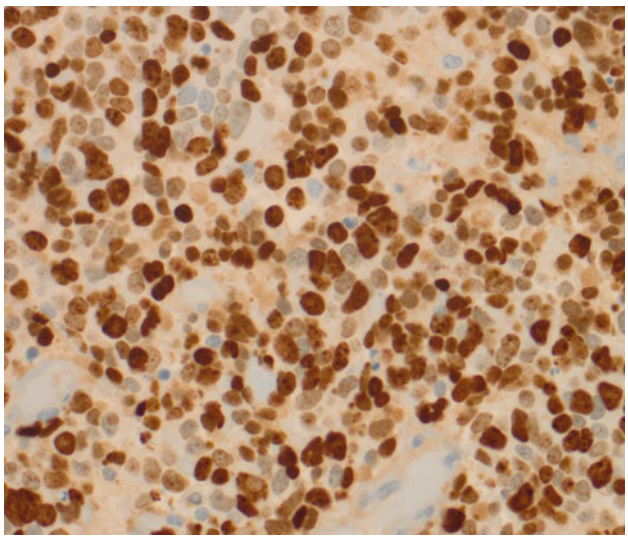

Fig. 5 Small cell carcinoma, ki-67 immunohistochemical staining

Conclusion

Small cell carcinoma is a difficult-to-treat cancer with early sensitivity to chemotherapy but a poor overall prognosis. Although this malignancy commonly originates in the lung, it can rarely be seen in other organs. An accurate pathologic diagnosis, while sometimes difficult, is necessary for prognostication and treatment. Our case is consistent with the clinical course seen in small cell carcinomas of other primary sites.

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