

# Subcutaneous metastasis of a pulmonary carcinoid tumor

## A case report

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### Abstract

**Rationale:** Carcinoid tumors are derived from neuroendocrine cells and are most frequently found in the gastrointestinal tract and bronchopulmonary system. They are generally characterized by an indolent clinical course but may in some instances spread to regional lymph nodes or to distant sites. Subcutaneous metastases of carcinoid tumors are extremely rare; there are only few cases reported in the literature and the site of the primary tumor was mainly the gastrointestinal tract. Also, the diagnosis of this type of lesions many years after the surgical resection of the pulmonary carcinoid (PC) could be a challenge for clinicians.

**Patient concerns:** A nonsmoker woman diagnosed with an atypical carcinoid stage IA2 maintained follow-up at our institution. Seven years later she incidentally detected a subcutaneous nodular lesion in the lumbar region.

**Diagnoses:** A positron emission tomography–computed tomography (PET/CT) was performed and showed pathological uptake of the referred lesion. An excisional biopsy was performed and with the support of immunohistochemistry the diagnosis of a subcutaneous metastasis from a pulmonary atypical carcinoid was made.

**Interventions:** The patient initiated chemotherapy with carboplatin plus etoposide and complied 4 cycles of treatment.

**Outcomes:** She maintained tight follow-up at our center and for 12 months there were no signs of relapse.

**Lessons:** This extremely rare case highlights the difficulties in the differential diagnosis and the importance of diagnostic tests as PET/CT and immunohistochemistry in the establishment of a diagnosis. Physicians should be aware of signs of skin metastasis from lung malignancies even if the prognosis is good or many years have passed since the surgical resection.

**Abbreviations:** 5-HIAA = 5-hydroxyindoleacetic acid, AC = atypical carcinoid, CrA = chromogranin A, CT = computed tomography, ENTS = European Neuroendocrine Tumour Society, NETs = neuroendocrine tumors, PC = pulmonary carcinoid, PET/CT = positron emission tomography–computed tomography, SRS = somatostatin receptor scintigraphy, TC = typical carcinoid, TNM = tumor, node, metastasis, TTF-1 = thyroid transcription factor-1.

**Keywords:** immunochemistry, PET/CT, pulmonary carcinoid, subcutaneous metastasis

## 1. Introduction

Pulmonary carcinoids (PCs) are rare tumors with an age-adjusted incidence rate ranging from 0.2 to 2/100,000 population/year in both United States and European countries and comprise approximately 2% of all primary lung cancers.<sup>[1]</sup>

The 2015 World Health Organization classification of pulmonary neuroendocrine tumors separates carcinoid tumors into typical and atypical.<sup>[2]</sup> Atypical carcinoid (AC) is the most uncommon PC tumor with a ratio between typical carcinoid (TC)

and AC of about 8–10:1.<sup>[1]</sup> Compared to TCs, ACs have a reported overall survival, after 5 and 10 years, of 78% and 67%, respectively.<sup>[3]</sup> Additionally, more advanced tumor stage for carcinoid tumors of the lungs and bronchi is associated with worse prognosis.<sup>[4]</sup> In one series 47% AC were included in stage I, 20% in stage II, 27% in stage III, and 7% in stage IV.<sup>[4]</sup> Despite the indolent nature and favorable prognosis of PCs, AC recurrence after surgery can occur.<sup>[5]</sup> The most common described sites for metastases from PCs are liver (37.0%), bone (33.3%), and mediastinal lymph nodes (22.2%).<sup>[6]</sup> Subcutaneous metastases from carcinoid tumors are very rarely encountered in clinical practice. To our knowledge there is only 1 study described of a subcutaneous metastasis of a PC although presenting concomitantly to other secondary lesions.<sup>[7]</sup> Also, skin nodules are a common clinical finding and most of cases are benign; therefore, when a skin nodule is discovered, several factors must be considered constituting a challenge for physicians.

We describe an extremely rare case of a metastatic pulmonary AC to subcutaneous tissue, many years after the diagnosis of the primary tumor. We also discuss PCs surveillance and useful diagnostic methods in this process.

## 2. Case report

A 30-year-old caucasian woman, nonsmoker and with no relevant medical or family history presented to her primary care doctor with weight loss in the previous 5 months and with

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persistent cough, sometimes with hemoptoic sputum. After a complete physical examination and a chest x-ray, a thoracic computed tomography (CT) was performed revealing a 2 cm lesion involving the right main bronchus without atelectasis and the patient was referred to our institution. A flexible bronchoscopy showed an obstructive lesion in the terminal main right bronchus and the technique was converted to rigid bronchoscopy. A therapeutic bronchoscopic procedure was done and the histological analysis of the lesion showed a well-differentiated neuroendocrine tumor (carcinoid) of the lung.

Both cranial and abdominal CT scans were negative and somatostatin receptor scintigraphy (SRS) with <sup>111</sup>In-labeled octreotide confirmed the presence of the pulmonary lesion and showed no other lesions. Serum levels of chromogranin A (CgA) and levels of 5-hydroxyindoleacetic acid (5-HIAA) in a 24-hour urine sample were within the normal range (2–9 mg/24 h). The patient was submitted to lobectomy of the right upper lobe with lymph node dissection. Microscopic evaluation revealed a well-differentiated neuroendocrine tumor, corresponding to a circumscribed insular and trabecular proliferation of cells with relatively abundant cytoplasm, rounded nuclei with fine and homogenous chromatin, without nucleoli, positive with antibodies for Cam5.2, CD56, chromogranin A, and synaptophysin. The mitotic count was 3 per 2 mm<sup>2</sup>, the KI67 index was 2% and no necrosis or lymphovascular was identified. The resection of the neoplasm was complete and the diagnosis of atypical lung carcinoid stage IA2 (TNM 8th edition) was established. The patient did not need adjuvant therapy. She maintained follow-up at our institution and performed regular CT with no evidence of recurrence of the disease. CgA and 5-HIAA levels were also monitored without any rise of its values.

Seven years later she incidentally detected a painless, small subcutaneous nodule, located on the back. Physical examination revealed a firm and well-circumscribed subcutaneous nodule that measured 0.5 to 1 cm. A soft tissue ultrasonography was performed and showed a hypoechoic nodule with 4 mm size suggestive of epidermoid cyst (Fig. 1).

<sup>68</sup>Ga-DOTANOC PET/CT revealed an involvement of subcutaneous lumbar lesion with no identification of another foci of pathological uptake (Fig. 2).

An excisional biopsy of this lesion was performed and showed subcutaneous adipose tissue occupied by a neoplasm with relatively well-defined borders, having a predominantly trabecular and cordonal pattern, in abundant desmoplastic stroma, comprising cells with weakly eosinophilic cytoplasm, round and smooth contoured nuclei, speckled chromatin, and inconspicuous

nucleoli. The immunohistochemical study revealed positivity of the neoplastic cells with antibodies for Cam5.2, chromogranin, synaptophysin, CD56, and TTF-1 (thyroid transcription factor 1). No staining was obtained with other markers (Ck7, Ck20, and Napsin-A). The tumor had no mitosis or necrosis and the KI67 index was 2%. The morphological features, together with the immunohistochemical profile (namely TTF-1 positivity) of the tumor, in the patient clinical context, were consistent with subcutaneous metastasis of a carcinoid tumor of the lung (Fig. 3).

The thoracic CT and bronchoscopy showed no evidence of recurrence of the tumor and a total colonoscopy was performed to exclude a primary carcinoid of the bowel. The patient initiated chemotherapy with carboplatin plus etoposide and complied 4 cycles of treatment. She maintained tight follow-up at our center and for 12 months there were no signs of relapse.

Informed consent for publication was given by the patient.

### 3. Discussion

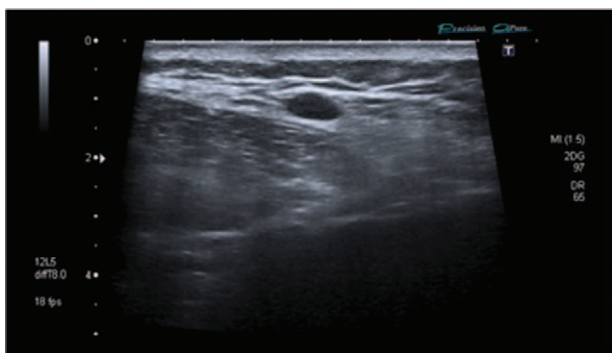
PC tumors are rare primary lung cancers that are known to have less aggressive behaviour than other lung cancers. Surgical removal is the treatment of choice for PCs. The surgical approach is dependent on the size, location and tissue type and the surgical techniques of choice are lobectomy or sleeve resection.<sup>[1]</sup> Systemic chemotherapy should be considered in patients with advanced unresectable progressive PC. Regimens showing antitumor activity against PC tumors include octreotide, doxorubicin/capecitabine, everolimus plus cisplatin, everolimus plus octreotide, and etoposide plus cisplatin.<sup>[8]</sup>

Patients with neuroendocrine tumors can be diagnosed in 10% of the cases based on a wide variety of paraneoplastic syndromes.<sup>[9]</sup> Biochemical testing should be carried out in consideration of clinical symptoms and features including as appropriate 24 hours urine 5-HIAA, adrenocorticotropic hormone, and growth hormone releasing hormone.<sup>[1]</sup> Our patient did not present evidence of paraneoplastic syndrome at diagnosis or at time of the progression.

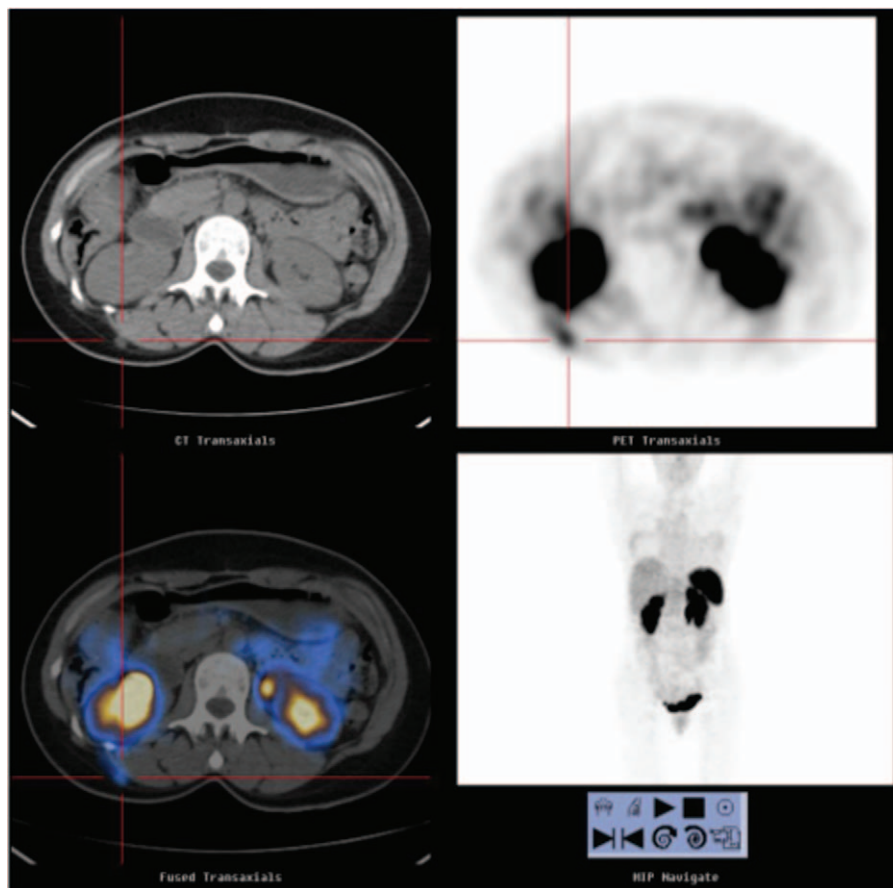
Carcinoids of the lungs and bronchi are staged in the same manner as more common lung carcinomas. In contrast to the 7th Edition of TNM Lung Cancer Staging, in the 8th Edition T1 was subdivided in mi, a, b, and c according to the size of the lesion as a progressive degradation of survival was observed for each 1 cm cut point.<sup>[10]</sup> Although, the tumor approach would not change.

Despite the indolent nature of carcinoid tumors, up to 26% of patients with atypical carcinoids may still experience recurrences.<sup>[5]</sup> The study by Lou et al about PCs showed higher recurrence rates and decreased survival among patients with atypical pathologic type and positive lymph node involvement compared to node-negative TCs.<sup>[5]</sup> Also, most relapses involved metastases to distant sites and the median time to recurrence was 22 months (range 2–83 months).<sup>[5]</sup> However, for both TC and AC, recurrence may not occur until many years later. In the same series the longest time to recurrence was more than 11 years,<sup>[5]</sup> but other series reporting recurrences up to 20 years were also referred by the authors.

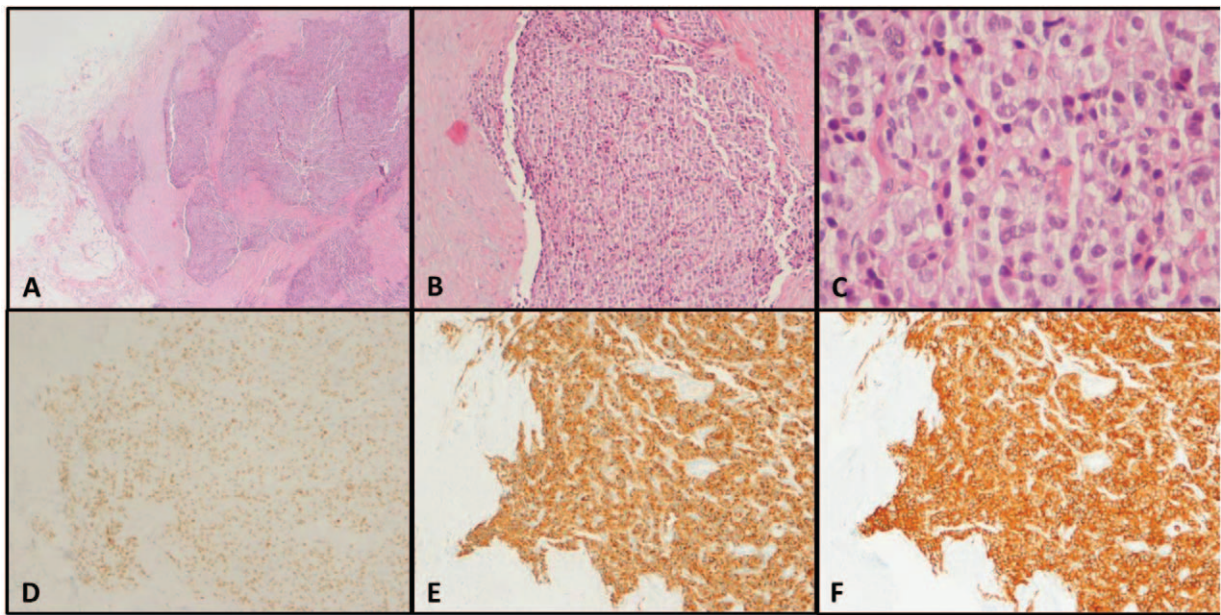
Surveillance for recurrences after surgical resection remains an important component of cancer care with a significant impact on survival, quality of life, and health care costs. Currently various published guidelines recommend routine surveillance with thoracic CT after surgical resection for nonsmall cell lung cancer.<sup>[11,12]</sup> Earlier detection of relapse may lead to prompt treatment and improved survival. Based on the high rate of metachronous lung malignancies and the detection power of



**Figure 1.** Soft tissue ultrasonography-subcutaneous hypoechoic 4 mm nodular lesion in the region of the right inferior flank.



**Figure 2.** <sup>68</sup>Ga-DOTANOC PET/CT—small nodular lesion in the subcutaneous tissue in the lumbar right region with discrete pathological uptake. PET/CT = positron emission tomography–computed tomography.



**Figure 3.** Expanding nodule on the subcutaneous adipose tissue with abundant fibrous/desmoplastic stroma (A) [HE, ×20]; solid area of the neoplasia (B) [HE, ×200]; neoplastic cells with abundant weakly eosinophilic cytoplasm and round nuclei with inconspicuous nucleoli a “salt-and pepper” chromatin pattern © [HE, ×400]; TTF-1 nuclear diffuse positivity (D) [TTF-1, ×100]; chromogranin-A strong and diffuse cytoplasmic positivity highlighting the cordonal and trabecular pattern of the neoplasia (E) [CgA, ×100]; synaptophysin strong and diffuse cytoplasmic positivity (F) [Syn, ×100]. TTF-1 = thyroid transcription factor-1.



routine CT scans, surveillance CT could detect most second primary lung cancers during asymptomatic, early stages. Recently, European Neuroendocrine Tumor Society (ENTS) guidelines on best practice for PC tumors recommended for ACs a close monitoring with CT imaging carried out 3 months post-surgery, then 6 monthly for 5 years and after 5 years yearly.<sup>[11]</sup> Nevertheless, most recurrences of carcinoid tumors are distant metastases (95%; 20 of 21) and surveillance limited to the chest or even the upper abdomen may not be effective in detecting relapse in other areas of the body.<sup>[5]</sup> In addition to location, a rational surveillance regimen must also consider the timing of recurrence and likelihood of events. Since recurrence may not occur until many years later some authors recommend follow-up care to be continued for at least 20 years.<sup>[12]</sup> However, if recurrences are rare, the utility of repeated imaging for such an extended period could be questionable. In this report the patient presented the metastasis 7 years after the diagnosis and under surveillance (annual CT in the last 6 years), which highlights the importance of a tight and prolonged follow-up of patients presenting atypical carcinoids. Also, 68Ga-DOTANOC PET/CT was an important part of the diagnostic process.

Nuclear medicine methods have been shown to play a relevant role in the evaluation of neuroendocrine tumors (NETs). Whole-body SRS has become an essential imaging technique for this type of tumors and therefore has been widely accepted and routinely used. Although SRS has shown high diagnostic accuracy for whole-body imaging,<sup>[13]</sup> there are some limitations for the evaluation of organs with a high physiologic uptake and for the detection of small lesions. Previous data showed that PET/CT with 68Ga-DOTA-NOC may be useful for the assessment of lung carcinoid patients, revealing in many patients the presence of disease at sites that could not be identified by conventional morphologic procedures and contribute to a better evaluation of disease.<sup>[12]</sup> In particular, PET/CT was more sensitive for the detection of malignancy at lymph nodes, liver and bone level than SRS.<sup>[14]</sup>

Subcutaneous metastases from carcinoid tumors are very rarely encountered in clinical practice. There are only a few cases reported in the literature, mainly originated from gastrointestinal tract<sup>[15–21]</sup> and, to our knowledge, only one from a PC.<sup>[7]</sup> Although this case illustrated a subcutaneous nodule as the initial presentation of an atypical lung carcinoid the patient presented a widely metastatic disease and a family history of cancer. Due to its rarity, the diagnosis of this type of metastasis may be difficult for clinicians and it is important to take in consideration possible others diagnosis. The differential diagnosis can include any primary or secondary tumor with neuroendocrine differentiation, including primary soft tissue carcinoid and soft tissue metastases from neuroendocrine carcinomas of different locations. Carcinoid tumors from the lung and gastrointestinal tract, and pancreatic endocrine tumors, have nearly identical histopathologic features, regardless of the site of origin. Thus, the differential diagnosis of a soft tissue carcinoid metastasis should take in consideration the location of the primary tumor. The presence of TTF-1 positivity in a carcinoid tumor can be of extreme help since, contrary to other neuroendocrine neoplasia such as carcinoids of other origins or small cell carcinoma from whatever origin, is indicative of a lung primary. Consequently, when dealing with metastatic well-differentiated neuroendocrine tumors, the utility of immunohistochemistry for thyroid TTF-1 cannot be underestimated, and its positivity can be determinant in search of the primary. Cai et al found that an immunopanel of CK7+/CK202/TTF-1+ was highly significantly associated with lung carcinoid tumors, with a sensitivity of 50% and a specificity

of 100%.<sup>[22]</sup> Although there are described differences in sensitivity, several studies have confirmed the specificity of TTF-1 in lung carcinoid tumors.<sup>[23–25]</sup> Further, TTF-1 may be more frequently expressed in atypical carcinoids,<sup>[23–25]</sup> particularly in those with a peripheral location. Our patient's lesion was positive for neuroendocrine markers and TTF-1, consistent with a metastasis from a lung carcinoid tumor.

In conclusion, we report an extremely rare case of an asymptomatic solitary lesion of the lumbar subcutaneous tissue found to be a metastasis from a pulmonary atypical carcinoid diagnosed and treated several years before. Primary and metastatic carcinoid tumors are often incidental findings thus are more frequently found when specifically sought. This case highlights the value of surveillance after atypical carcinoid tumor surgery and the usefulness of PET/CT and immunohistochemistry to make a diagnosis. Physicians should be aware of signs of skin metastasis from lung malignancies even if the prognosis is good or many years have passed since the surgical resection.

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