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 a 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 refered 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: immunohistochemistry, 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.\textsuperscript{[1]} The 2015 World Health Organization classification of pulmonary neuroendocrine tumors separates carcinoid tumors into typical and atypical.\textsuperscript{[2]} Atypical carcinoid (AC) is the most uncommon PC tumor with a ratio between typical carcinoid (TC) and AC of about 8–10:1.\textsuperscript{[1]} Compared to TCs, ACs have a reported overall survival, after 5 and 10 years, of 78% and 67%, respectively.\textsuperscript{[3]} Additionally, more advanced tumor stage for carcinoid tumors of the lungs and bronchi is associated with worse prognosis.\textsuperscript{[4]} In one series 47% AC were included in stage I, 20% in stage II, 27% in stage III, and 7% in stage IV.\textsuperscript{[4]} Despite the indolent nature and favorable prognosis of PCs, AC recurrence after surgery can occur.\textsuperscript{[5]} The most common described sites for metastases from PCs are liver (37.0%), bone (33.3%), and mediastinal lymph nodes (22.2%).\textsuperscript{[6]} 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.\textsuperscript{[7]} 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 women, 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
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 111In-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/24h). 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 mm², 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 hypoechochogenic nodule of 4 mm size suggestive of epidermoid cyst (Fig. 1).

![Figure 1. Soft tissue ultrasonography:subcutaneous hypoechochogenic 4 mm nodular lesion in the region of the right inferior flank.](image)

68Ga-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, sinaptophysin, 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.[11] Systemic chemotherapy should be considered in patients with advanced unresectable progressive PC. Regimens showing antitumor activity against PC tumors include octreotide, doxorubicin/capcitabine, everolimus plus cisplatin, everolimus plus octreotide, and etoposide plus cisplatin.[8]

Patients with neuroendocrine tumors can be diagnosed in 10% of the cases based on a wide variety of paraneoplastic syndromes.[9] Biochemical testing should be carried out in consideration of clinical symptoms and features including as appropriate 24hours urine 5-HIAA, adrenocorticotropic hormone, and growth hormone releasing hormone.[11] 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.[10] 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.[5] 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.[5] Also, most relapses involved metastases to distant sites and the median time to recurrence was 22 months (range 2–83 months).[5] 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,[5] 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.[11,12] Earlier detection of relapse may lead to prompt treatment and improved survival. Based on the high rate of metastrophic lung malignancies and the detection power of
Figure 2. 68Ga-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 (C) [HE, ×400]; TTF-1 nuclear diffuse positivity (D) [TTF-1, ×100]; chromogranin-A strong and diffuse cytoplasmatic positivity highlighting the cordonal and trabecular pattern of the neoplasia (E) [CgA, ×100]; synaptophysin strong and diffuse cytoplasmatic 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 Tumour 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.[11] 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.[15] 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.[12] 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,[13] 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.[12] In particular, PET/CT was more sensitive for the detection of malignancy at lymph nodes, liver and bone level than SRS.[14]

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[11–21] and, to our knowledge, only one from a PC.[7] Although this case illustrated a subcutaneous nodule as the initial presentation of an atypical lung carcinoid the patient presented a wide 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/TF1-1+ was highly significantly associated with lung carcinoid tumors, with a sensitivity of 50% and a specificity of 100%.[22] Although there are described differences in sensitivity, several studies have confirmed the specificity of TTF-1 in lung carcinoid tumors.[23–25] Further, TTF-1 may be more frequently expressed in atypical carcinoids,[23–25] 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.

References

[1] Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumour Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol 2015;26:1604–20.
[2] Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. International Agency for Research on Cancer, Lyon:2015.
[3] Garcia-Yuste M, Matilla JM, Cueto A, et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multicentric Study of Neuroendocrine Tumours of the Lung. Eur J Cardiothorac Surg 2007;31:192–7.
[4] Lim E, Yap YK, De Stavola BL, et al. The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. J Thorac Cardiovasc Surg 2005;130:969–72.
[5] Lou F, Sarkaria J, Pietranza C, et al. Recurrence of pulmonary carcinoid tumors after resection: implications for postoperative surveillance. Ann Thorac Surg 2013;96:1156–62.
[6] Bhoasale P, Shah A, Wei W, et al. Carcinoid tumours: predicting the location of the primary neoplasm based on the sites of metastases. Eur Radiol 2013;23:400–7.
[7] Yua R, Wolina E, Fanb X. Subcutaneous nodule as initial presentation of atypical lung carcinoid. World J Oncol 2010;1:204–7.
[8] Chong C, Wirth L, Nishino M, et al. Chemotherapy for locally advanced and metastatic pulmonary carcinoid tumors. Lung Cancer 2014;86:241–6.
[9] Jung I, Guzru S, Balasa R, et al. A coin-like peripheral small cell lung carcinoma associated with acute paraneplastic axonal Guilain–Barre-like syndrome. Medicine (Baltimore) 2015;94:e910.
[10] Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol 2015;10:1009–1003.
[11] Jacobson FL, Austin JH, Field JK, et al. Development of The American Association for Thoracic Surgery guidelines for low-dose computed tomography scans to screen for lung cancer in North America: recommendations of The American Association for Thoracic Surgery Task Force for Lung Cancer Screening and Surveillance. J Thorac Cardiovasc Surg 2012;144:25–32.
[12] Dettetteeb F. Management of carcinoid tumors. Ann Thorac Surg 2010;89:998–1005.
[13] Ramage JK, Davies AH, Ar idi J, et al. UKNET work for neuroendocrine tumours. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours. Gut 2005;54(suppl 4)iv1–6.
[14] Ambrosini V, Castellucci P, Rubello D, et al. 68Ga-DOTANOC: a new PET tracer for evaluating patients with bronchial carcinoid. Nucl Med Commun 2009;30:281–6.
[15] Dalla Valle R, Borti C, Milione M, et al. Solitary facial metastasis of an ileal carcinoid. Acta Biomed 2003;74:47–9.
[16] Naschitz JE, Yeshurun D, Nash E, et al. Cervical soft tissue metastasis of typical carcinoid tumor preceding diagnosis of ileal primary by 4 years. Am J Gastroenterol 1992;87:1665–8.
[17] Quan GM, Pitman A, Slavin J, et al. Soft tissue metastasis of carcinoid tumour: a rare manifestation. ANZ J Surg 2004;74:164–6.
[18] Caobelli F, Pizzocaro C, Quartuccio N, et al. Unusual widespread metastatic subcutaneous lesions in a patient with ileal carcinoid evidenced by 68Ga-DOTATOC PET/CT. Clin Nucl Med 2014;39:391–2.
[19] Tiktinsky E, Horne T, Agranovich S, et al. Intramuscular metastasis of carcinoid tumor: a rare manifestation. Clin Nucl Med 2008;33:484Y485.
[20] Caobelli F, Bertagna F, Panarotto MB, et al. An unusual muscular metastasis in a patient affected by ileal carcinoid imaged with a 111In-pentetreotide SPECT/CT scan and confirmed by biopsy. Clin Nucl Med 2011;36:696Y697.
[21] Seven B, Varoglu E, Cavir K, et al. Chest wall metastasis of ileal carcinoid tumor detected with In-111 octreotide scan. Clin Nucl Med 2006;31:552–3.
[22] Cai YC, Banner B, Glickman J, et al. Cytokeratin 7 and 20 and thyroid transcription factor 1 can help distinguish pulmonary from gastrointestinal carcinoid and pancreatic endocrine tumors. Hum Pathol 2001;32:1087–93.
[23] Du EZ, Goldstraw P, Zacharias J, et al. TTF-1 expression is specific for lung primary in typical and atypical carcinoids: TTF-1-positive carcinoids are predominantly in peripheral location. Hum Pathol 2004;35:825–31.
[24] Agoff SN, Lamps LW, Philip AT, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol 2000;13:238–42.
[25] Lin X, Saad RS, Luckasevic TM, et al. Diagnostic value of CDX-2 and TTF-1 expressions in separating metastatic neuroendocrine neoplasms of unknown origin. Appl Immunohistochem Mol Morphol 2007;15:407–14.