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Skin metastasis from typical carcinoid tumor of the lung

Carcinoids are neuroendocrine tumors that may arise within any organ, although they are more commonly found in the gastrointestinal tract and in the bronchopulmonary tract. They are generally characterized by an indolent clinical course but may in some instances metastatise to regional lymph nodes or to distant sites. We herein describe a rather infrequent case of a 60-year-old man with a skin metastasis from a typical carcinoid of the lung. We discuss the histopathological and immunohistochemical features in the context of previous literature and comment issues related to difficulties in the differential diagnosis. Dermatopathologists should be familiar with the metastatic carcinoid profile in order to avoid potential misdiagnoses and to properly address the patient management when the skin metastasis represents the first manifestation of an internal disease.

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Carcinoids are neuroendocrine tumors that may arise within any organ, although they are more commonly found in the gastrointestinal tract (about 65%) and in the bronchopulmonary tract (about 25%).[1] They are thought to originate from cells of the so called dispersed neuroendocrine system that are widely distributed in the body. They are generally characterized by an indolent clinical course but may in some instances metastatise to regional lymph nodes or to distant sites. The clinical behaviour of carcinoid tumors is difficult to predict on the basis of morphological features. Differences in prognosis have been found concerning lung carcinoid tumors. According to the latest World Health Organization classification system of tumors of the lung,[2] carcinoids are distinguished in two categories, typical and atypical, on the basis of morphological criteria (number of mitoses and/or presence of necrosis). Atypical carcinoid (AC) tumors have been found to have a more aggressive clinical course than typical carcinoids (TC).[3]

Carcinoid metastases to the skin and subcutaneous (s.c.) tissues are considered to be a late manifestation of the disease. They are very rare, with only single reports in the literature.[4–26] Since changes in the classification systems occurred over the last decades they do not allow a clear definition of previously described cases, nonetheless, an accurate review of the literature suggests that both TC and AC may metastasise to the skin. Because the prognosis of patients with advanced disease has been improved in recent years, new metastatic patterns, including cutaneous metastases, may be found more frequently. The diagnosis of a skin metastasis from a carcinoid tumor may be difficult especially for dermatopathologists, who are not familiar with carcinoid tumors.

We herein describe a case of skin metastasis from a pulmonary TC, in the context of previous literature and comment issues related to difficulties in the differential diagnosis.

Case report

A 60-year-old man presented with palpitations, vague chest pain, some exercise-induced dyspnoea and haemoptysis. He also referred a several months history of episodic flushing of the skin. The patient was a heavy smoker since many years. A chest radiograph was performed and a centrally located opacity with mediastinal enlargement was detected.

A subsequent computerized tomography (CT) scan showed in the upper left lobe the presence of an ill-defined 4.5 × 3.5 cm, roundish, hypodense mass, with low contrast enhancement; mediastinal nodal involvement was also described. Pleural effusion was absent. A bronchoscopy was performed and a biopsy showed a well-differentiated neuroendocrine tumor consistent with TC. Bone scintigraphy showed uptake in the vertebral column, the ribs and the iliac crest, which were considered multiple skeletal secondary lesions. Serum levels of Chromogranin A (CgA) were elevated at 6523 ng/ml (normal ≤ 123). Positron emission tomography scanning using ^{18}F-labeled fluorodeoxyglucose confirmed the presence of the pulmonary lesion. Somatostatin receptor scintigraphy with ^{111}In-labeled octreotide detected the presence of lung, mediastinal and bone lesions and showed multiple liver metastases (Fig. 1). Cranial CT scan was negative. The patient underwent somatostatin analog therapy with octreotide in the form of s.c. injections of the immediate release formulation for 14 days, followed by intramuscular injections of the long-acting release formulation.

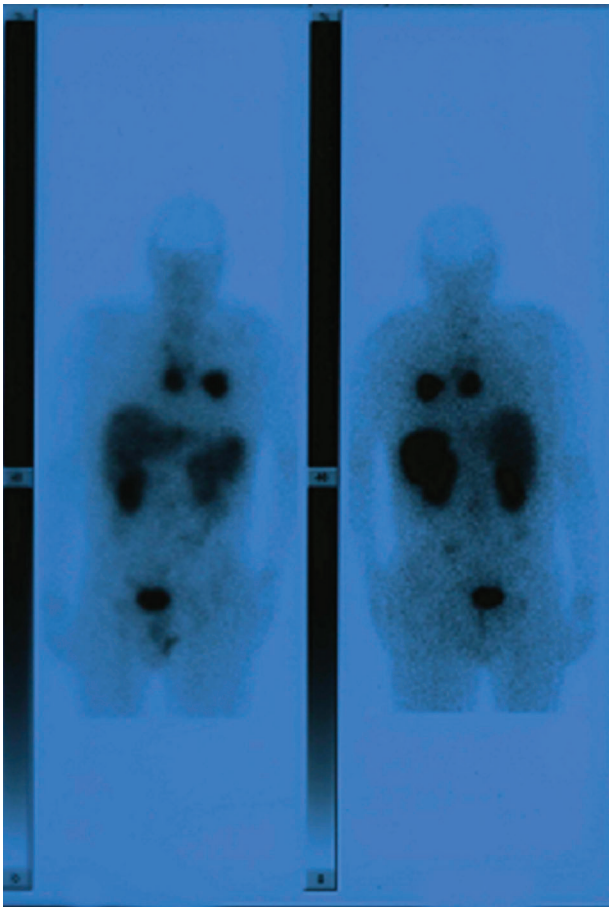

Fig. 1. Somatostatin receptor scintigraphy with ^{111}In-labeled octreotide detected the presence of lung, mediastinal and liver metastases.

After 30 days the patient presented a strong attenuation of the flushing and the CgA serum levels were reduced to 2855 ng/ml.

During a follow-up clinical examination, the patient reported the presence of a rapidly-growing, painless, skin nodule, located on the back. The nodule was violaceous-red in colour, firm at palpation and measured 2.5 × 1 cm. An excisional biopsy was performed.

The skin specimen was fixed in 10% buffered formalin and paraffin embedded. Sections 5 μm in thickness were stained with hematoxylin and eosin for conventional histopathological examination. Immunohistochemical studies were performed on representative sections of the tumor. Pre-diluted antibodies were used for cytokeratins AE1/AE3, CAM 5.2, CK7, CK20, CD56, synaptophysin, chromogranin, neuron specific enolase (NSE) and thyroid transcriptional factor-1 (TTF-1) (all from Ventana Medical Systems, Tucson, AZ, USA). The reaction product was detected with 3,3-diaminobenzidine chromogen. Appropriate positive and negative controls were employed throughout.

Histopathological examination showed an ill-defined dermal proliferation of medium-sized monomorphous epithelioid cells that focally involved the s.c. fat (Fig. 2A). The tumor cells were arranged in insulae of variable size and shape with an organoid and trabecular pattern of growth (Fig. 2B). Cytologically, tumor cells displayed a scant to moderate, eosinophilic granular cytoplasm, the nuclei were round to oval, with a finely granular chromatin pattern. Vascular invasion was also evident. Mitoses were < 1 per 10 High Power Field (HPF). The immunohistochemical profile of the tumor was characterized by strong and diffuse positivity for AE1/AE3, CAM 5.2, CgA and synaptophysin (Fig. 3). The staining pattern for NSE and CK7 was weak and focal. CD56, CK20 and TTF-1 were found to be negative.

The original slides of the pulmonary lesion were reviewed and showed overlapping histopathological and immunohistochemical features (Fig. 2C). The mitotic activity was low (< 2 per 10 HPF) and no necrosis was observed, thus confirming the diagnosis of typical carcinoid tumor. A final diagnosis of skin metastasis of lung carcinoid tumor was made.

Discussion

Cutaneous metastases from carcinoid tumors are only occasionally encountered in clinical practice. To the best of our knowledge, only 28 well-documented cases have been reported so far in the literature.[4–26] Mean age of reported patients was 56 years (range: 35–80 years) with no difference in gender distribution. The site of the primary tumor

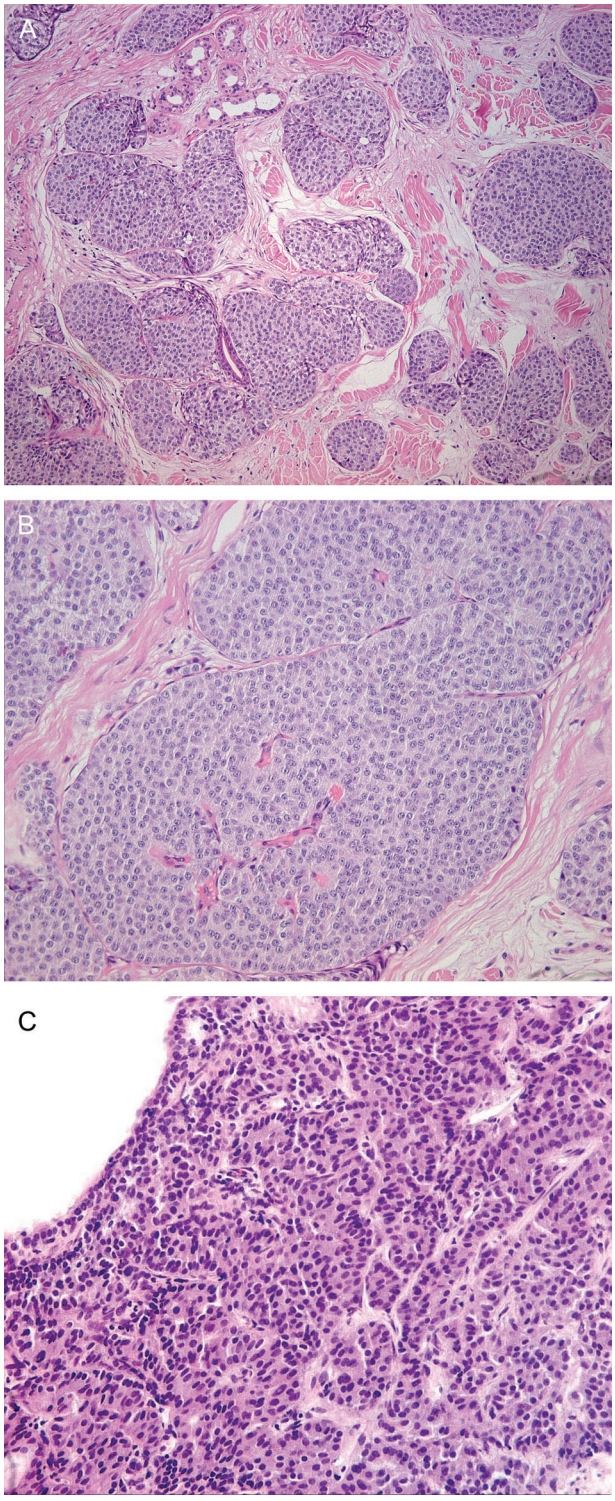

Fig. 2. Histopathological examination showed an ill-defined dermal proliferation of medium-sized monomorphous epithelioid cells with an organoid and trabecular pattern of growth (A). The tumor cells were arranged in insulae of variable size and shape and displayed a scant to moderate, eosinophilic granular cytoplasm, the nuclei were round to oval, with a finely granular chromatin pattern (B). Histopathology of the bronchial typical carcinoid tumor with trabecular and organoid pattern (C).

was the bronchus in 13 (46.4%) cases [9–15,18,21,22,25] the gastrointestinal tract in 8 (28.5%) cases, [4–8,23,26], the larynx in 2 (7.1%) cases,[20,24] and the testis in 1 (3.5%) case.[19] In the remaining four reported cases the primary site of the tumor was unknown.[16,17,25] In bronchial carcinoids, cutaneous metastases were found to be present at the time of diagnosis in five cases, whereas, in two cases, a metastatic nodule was the first clinical evidence indicative of the tumor.[18,21,22] Skin carcinoid metastases have been described as erythematous/violaceous firm, often multiple, nodules, ranging from 0.3 to 3 cm in size. Most lesions were asymptomatic, although painful and ulcerating nodules have been reported as well.[20–23,25] The clinical and laboratory findings of the carcinoid syndrome have been described only in a few cases. When metastases were reported in tissues other than the skin, they were mainly referred to the liver and lungs.

The differential diagnosis includes any primary or secondary tumor with neuroendocrine differentiation, including primary cutaneous carcinoid, primary cutaneous neuroendocrine (Merkel cell) carcinoma, primary malignant peripheral primitive neuroectodermal tumour (PNET)/extraskeletal Ewing sarcoma (ES) and skin metastases from neuroendocrine carcinomas of different locations. In addition, the recently described sebaceous neoplasms with carcinoid-like pattern may also enter the differential diagnostic problem.

Primary cutaneous carcinoid tumors are exceedingly rare, with only seven cases reported to date.[27–33] Although skin metastases are more commonly described as multiple lesions, the histological and immunohistochemical features of primary and secondary carcinoids overlap, thus an extensive and accurate clinical investigation is mandatory. Primary carcinoids are generally associated with a good prognosis, despite mitotic activity.[33] However, a lymph node metastasis has been reported only in one case.[34]

In Merkel cell carcinoma a trabecular growth pattern, ribbons or festoons, that may mimic a carcinoid tumor may be observed. However, the overall pattern of growth of this tumor is characterized by diffuse sheets and solid nests of neoplastic cells. The cytological features of Merkel cell carcinoma are of clear high grade malignancy (small blue cell neoplasm), the mitotic rate is high and necrosis is often present. Moreover, Merkel cell carcinomas are typically CK20-positive, unlike carcinoid tumors. PNET/ES are malignant small blue round cell tumors which exhibit varying degrees of neuroectodermal differentiation. The neoplastic cells are arranged in nests, trabeculae, lobules and sheets. The cytologic features, the high apoptotic rate, the high mitotic activity, and the

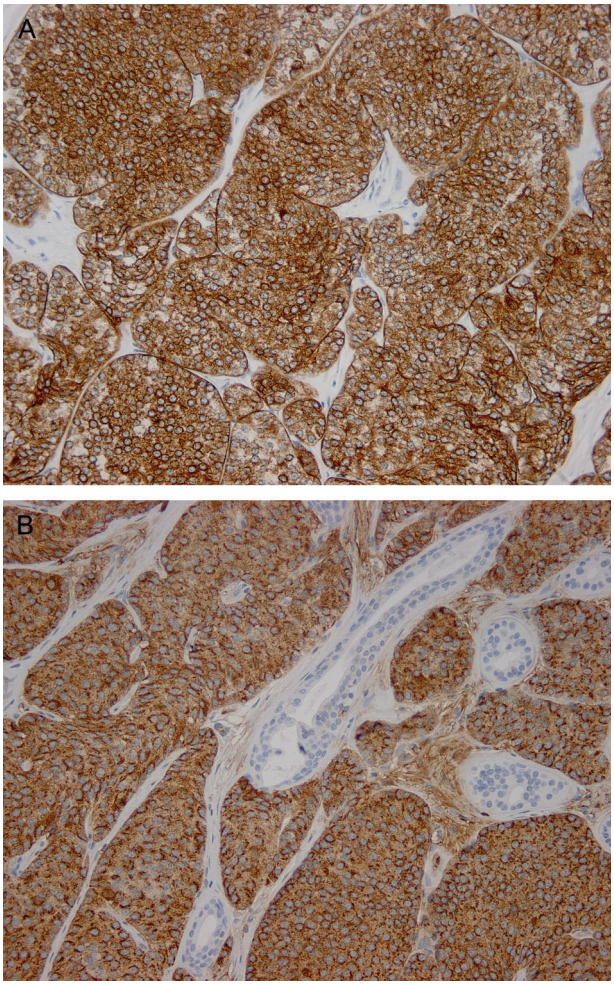

Fig. 3. The skin tumor showed strong and diffuse immunoreactivity for AE1/AE3 (A) and chromogranin A (B).

presence of necrosis together with the immunohistochemical profile of the tumor (strong and diffuse CD99 positivity, focal, aberrant cytokeratin-positivity and negative staining for chromogranin) make the differential diagnosis with carcinoid tumors quite straightforward.

When dealing with metastatic neuroendocrine carcinomas, the morphological appearance of a high grade tumor facilitates the differential diagnosis. The immunohistochemical use of TTF-1 may be of particular importance in search of the primary location of the tumor. TTF-1 is a highly sensitive and specific marker of neuroendocrine carcinomas of lung (small cell carcinoma and large cell neuroendocrine carcinoma) and is negative in neuroendocrine carcinomas of other sites and generally not expressed in carcinoid tumors.

The lesions that mostly resemble the morphological features of carcinoid tumors are the recently described sebaceous neoplasms with carcinoid-like pattern.[35] These neoplasms comprise both sebaceous carcinoma and sebaceoma characterized by neoplastic cells arranged in a trabecular and ribbon-like pattern, with or without rosettes/pseudorosettes. Sebaceous differentiation, in the form of mature sebocytes, may not be apparent, especially in sebaceous carcinomas. The term carcinoid-like pattern is used to indicate the endocrine morphology of these tumors that seems to be closely related to the well known rippled and labyrinthine/sinusoidal patterns. However, no neuroendocrine differentiation of these tumors has been observed by means of immunohistochemical, histochemical or ultrastructural studies. Thus, the search for sebaceous differentiation is recommended in cases of cutaneous tumors that are microscopically consistent with a carcinoid but are negative for endocrine markers by immunohistochemistry. A recent study by Liang et al.[36] showed positive immunostaining with the D2-40 monoclonal antibody in both sebaceous carcinomas and sebaceomas: in the former, the authors found diffuse positive immunoreactivity in the basaloid cells whereas in the latter, D2-40 immunostaining was found to be positive in the basaloid cells at the basal layer of tumor lobules and negative in the differentiated vacuolated cells. These results suggest the use of D2-40 in differentiating sebaceous neoplasms with carcinoid-like pattern from carcinoid tumors since immunoreactivity for this antibody has not yet been described in neuroendocrine tumors.

In conclusion, we report a case of cutaneous metastasis from a TC tumor of the lung. Although skin metastases of carcinoid tumors are rare, and may represent a diagnostic challenge, histopathological diagnosis may be easily obtained if a well documented clinical history is provided. However, it is worth noting that skin carcinoid metastases may represent the first clinical manifestation of a carcinoid tumor originated in other organs. Thus, dermatopathologists should be familiar with their histopathological features and immunohistochemical profile in order to avoid potential misdiagnoses and to properly address the patient management when the skin metastasis represents the first manifestation of the internal disease.

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