Cutaneous Metastasis from Laryngeal Atypical Carcinoid

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Carcinoid tumors are primarily regarded as tumors of the appendix and small intestine, but they have been shown to arise from almost any tissue derived from the primitive gut, including its respiratory diverticulum. Cutaneous metastasis from carcinoid tumors is distinctly rare, and only a few cases have been documented. In this report, we present one case of laryngeal atypical carcinoid tumor with skin metastasis. The diagnosis of metastatic carcinoid to the skin was established by clinical history, histopathology and immunocytochemical methods including positive stains of chromogranin, NSE, synaptophysin and cytokeratin AE1/AE3, etc.. To our knowledge, this is the first reported case of a laryngeal atypical carcinoid with skin metastasis in Taiwan. We disclose the aggravated behavior of the laryngeal atypical carcinoid tumor and remind dermatologists to be aware of the possibility of cutaneous metastasis, even if the primary tumor is a carcinoid.(Dermatol Sinica 23: 96-100, 2005)

Key words: Carcinoid, Cutaneous metastases, Larynx

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INTRODUCTION

Carcinoid tumors arise from neuroendocrine cells and commonly present with carcinoid syndrome, the cutaneous manifestations of which include episodic flushing, patchy cyanosis, telangiectasia, and pellagra-like skin lesions. Malignant carcinoid tumors, although rare, may metastasize to the skin. Primary carcinoids giving rise to cutaneous metastases occur most frequently in the bronchi but have been reported in various sites, including the small intestines, sigmoid, colon, pancreas, stomach, thymus, and thyroid. Herein we present an unusual case with a laryngeal atypical carcinoid tumor, in which skin metastasis occurred soon after the primary tumor was diagnosed and treated.

CASE REPORT

A 55-year-old male with a history of heavy smoking, presented with one rapid-growing, painless, 2 x 2 cm sized, flesh-colored nodule on his back for two weeks. The skin lesion was rubbery and non-movable (Fig. 1). There was no history of wheezing, diarrhea, or flushing episodes.

In the previous year, the patient had undergone left hemiepiglotectomy for the laryngeal atypical carcinoid tumor. The initial presentation is sore throat and hoarseness for 5 months. The laryngeal fiberoptic scope revealed an ulcerative and indurative mass over left epiglottis near aryepiglottic(A-E) fold and biopsy was done by flexible laryngovideoscopy. Pathological report revealed moderate differentiated neuroendocrine carcinoma (atypical carcinoid). Then the patient was admitted for left hemiepiglotectomy with modified neck dissection. One month after the procedure, several palpable cervical lymph nodes were noted. It was confirmed metastasis histologically. The patient was later treated with adjuvant radiotherapy using 3D conformal technique for a total dose of 6120 cGy in 34 sessions. The patient was disease-free until three months before our examination when one flesh-colored subcutaneous nodule appeared on his lower back. A biopsy of the skin lesion was performed. Histological examination showed a well-demarcated tumor located in the deep dermis and subcutis (Fig. 2). It consisted of large cells growing in nest and cord patterns (Fig. 3). The tumor cells were characterized with ample eosinophilic cytoplasm and large round to oval nuclei with “salt and pepper” chromatin. Mitotic figures and nuclear pleomorphism were sometimes noted (Fig. 4). Immunohistochemical stains were positive for cytokeratin AE1/AE3, NSE, chromogranin, and synaptophysin, proving the neuroendocrine origin of the metastatic...
cells (Fig.5). We made a diagnosis of cutaneous metastasis according to the compatible pathologic findings with the original neoplasm. Serum serotonin and urine 5-HIAA were not applicable to our patient, because he did not present symptoms of carcinoid syndrome. The patient later received a generalized survey for metastasis. A series of work-up showed multiple metastases at the liver and lumbar spine. Therefore, palliative chemotherapy with etoposide and cisplatinum was initiated. However, the patient’s condition deteriorated rapidly within a week, eventually dying due to sepsis. Death occurred within only 3 months since detecting cutaneous metastasis.

**DISCUSSION**

The frequency of skin metastases from internal malignancy varies from 0.7% to 10% in patients with cancer. The most common primary sources of metastasis are the breast in women and the lung in men. Skin metastasis from a carcinoid tumor is very rare. There have been no reported cases of carcinoid tumors with skin metastasis over several large series.

Carcinoids are well to moderately-differentiated neuroendocrine carcinomas and are a part of amine precursor uptake and decarboxylation (APUD) cell systems. They are characterized by the secretion of vasoactive peptide hormones and biogenic amines, which lead to the well-known “carcinoid syndrome.”

and Sandler classified these tumors into foregut, midgut, and hindgut derivatives. The larynx, trachea, and bronchi are all from the foregut respiratory diverticulum. Therefore, carcinoid tumors can occur in the larynx, although rarely. It was first described by Goldman et al. in 1969.

Carcinoid metastases to the skin are very uncommon. Primary carcinoid tumors have been identified in the bronchi, small intestine, sigmoid colon, pancreas, thymus, and thyroid. Up to date, we only found three sporadic...
cases of cutaneous metastases from laryngeal carcinoids in the English literature. Two patients were females, and one patient was a male. The mean age was 65 years. The metastatic locations included the chest, back, scalp and multiple sites, which were not specifically described in one report. Cutaneous metastasis appeared 15 months and five years after the primary tumor, respectively, while in the remaining case it was the first presentation sign. The patients died within 33, 58 and 66 months after primary diagnosis.

The diagnosis of carcinoid tumor is based upon the histologic appearance in the light microscopy and is strongly supported by immunohistochemical studies. Metastatic carcinoids may have the same or more anaplastic pathologic features than the primary tumor. The tumor cells are organized in nests, cords, sheets, glandular or rosette-like structures, diffusely infiltrating hyalinized and well-vascularized connective tissue stroma, which sometimes contains amyloid. The tumor cells have small, rounded nuclei with abundant eosinophilic cytoplasm containing numerous delicate granules. The centrally or sometimes eccentrically placed nucleus is characterized by “salt and pepper” chromatin. All the above histopathological findings could be observed in our case. Atypical carcinoid differs from typical carcinoid by presenting with cellular atypia and pleomorphism, higher mitosis counts, and tumor necrosis. Clinically, atypical carcinoids are likely to form distant metastases, whereas typical cases are not. In the larynx, atypical carcinoid tumors occur much more frequently than typical carcinoids.

Carcinoid tumors belong to a group of neuroendocrine tumors of epithelial origin, i.e. neuroendocrine carcinomas. They are positive for pan-keratin markers, NSE, chromogranin, synaptophysin, calcitonin and Grimelius staining in immunohistochemical studies. Tumor entities important in the differential diagnosis of metastatic cutaneous carcinoids include Merkel cell carcinoma, cutaneous metastasis from medullary carcinoma of the thyroid, undifferentiated squamous cell carcinoma, poorly differentiated primary eccrine carcinoma, and malignant melanoma. In most cases, carcinoid tumors can be differentiated by hematoxylin and eosin stained sections by the characteristic histopathologic features mentioned above. The distinction between metastatic cutaneous carcinoids and Merkel cell carcinoma is the most important. Chan et al. reported that cytokeratin 20 is a useful marker in distinguishing between them. In addition, the presence of an intraepidermal component would favor Merkel cell carcinoma. Involvement of the deep dermis and multiple skin sites favor a metastatic lesion. When markers are inconclusive for differential diagnosis, electron microscopy should be performed to establish the correct diagnosis.

Carcinoid syndrome occurs in about 5% of patients with carcinoid tumors. Characteristic manifestations include episodic flushing, asthma-like bronchoconstriction, diarrhea, ascites and right-sided cardiac valvular disease. However, reported laryngeal carcinoids have been clinically nonfunctional, as in our patient. The absence of a clinically recognizable syndrome may be related to the production of biologically inactive products, rapid degradation, intermittent release of biologically active products or the lack of recognition of subtle clinical symptomatology.

Generally, carcinoid tumors are often indolent tumors. Compared to carcinoids in other organs, laryngeal carcinoid tumors tend to have a relatively malignant clinical course because atypical carcinoid tumors occur much more frequently. More than 40% of cases have been reported to have positive cervical lymph nodes, and about 66% had distant metastases at diagnosis. Cutaneous metastases were reported in approximately 22% of the cases. Metastatic neuroendocrine carcinomas in the skin are most commonly derived from lung cancers and other cancers of foregut origin. Therefore, atypical laryngeal carcinoids should always be ruled out when investigating cutaneous metastases from an unknown primary tumor with neuroendocrine features.
After detection of a metastatic neuroendocrine carcinoma, the survival time of patients is reported ranging from 0 months to 4 years.\textsuperscript{22, 24} In our case, there was only a three-month survival period. Since cutaneous metastases are always found together with lymph node and organ metastases,\textsuperscript{8} systemic serial workups are necessary. We believe cutaneous metastasis was the first sign representing tumor recurrence in this patient. Liver and bony metastases were later found in subsequent generalized surveys.

In conclusion, carcinoid tumors are most encountered by gastroenterologists, oncologists, or surgeons. We present a rare case of cutaneous metastatic atypical carcinoid originating from the larynx, which demonstrated an aggravated clinical course without exhibiting carcinoid syndrome. We would remind all dermatologists to keep carcinoid tumors with its cutaneous manifestations in mind. Discovery of carcinoid tumors in skin biopsies should alert us to the possibility of metastasis of foregut origin.

REFERENCES