Subcutaneous metastasis from an atypical pulmonary carcinoid tumor

James T Pathoulas[1*] BA, Kelly E Flanagan[1*] MS, Chloe J Walker[1] MHS MD, Amy Ly[2] MD, Katherine M Krajewski[3] MD, Isabel Pupo Wiss[1] BS, Maryanne M Senna[1] MD

[*]Authors contributed equally

Affiliations: [1]Department of Dermatology, Harvard Medical School-Massachusetts General Hospital, Boston, Massachusetts, USA, [2]Department of Pathology, Harvard Medical School-Massachusetts General Hospital, Boston, Massachusetts, USA, [3]Department of Radiology, Harvard Medical School-Brigham And Women's Hospital, Boston, Massachusetts, USA

Corresponding Author: Maryanne M Senna MD, Massachusetts General Hospital, Department of Dermatology, 50 Staniford Street, Suite 200, Boston, MA 02114-2517, Tel: 617-726-2914, Email: msenna@partners.org

Abstract

Pulmonary carcinoid tumors are uncommon neuroendocrine tumors that rarely metastasize to the skin. We report the case of a 71-year-old woman with a longstanding history of primary atypical pulmonary carcinoid tumor who presented with a new tender cutaneous nodule. Immunostaining of the nodule was consistent with metastatic atypical carcinoid tumor of the skin including positive staining for neuroendocrine markers chromogranin and synaptophysin. Dermatologists should consider cutaneous neuroendocrine metastasis when evaluating new nodules in patients with stable pulmonary carcinoid tumors or in those with concomitant concerning respiratory symptoms.

Keywords: atypical, cutaneous, cutaneous, metastasis, metastatic, neoplasm, neuroendocrine, subcutaneous, tumor

Introduction

Pulmonary carcinoid tumors (PCs) are uncommon neuroendocrine tumors, representing 1-2% of all primary lung cancers [1]. Pulmonary carcinoid tumors are classified as typical or atypical carcinoids. Atypical PCs are more clinically aggressive and rare than typical PCs [1,2]. Histologically, atypical PCs are pleomorphic, have a greater mitotic burden than typical PCs, and can have associated necrosis [3].

Pulmonary carcinoid tumors typically present in the fifth decade of life with symptoms secondary to structural obstruction and tumor invasion including hemoptysis, cough, and dyspnea [1,2]. Bronchial PCs can have serotonergic secretory activity contributing to the characteristic but rare 'carcinoid syndrome' with symptoms including cutaneous flushing, diarrhea, and asthma attacks. However, 25% of PCs are discovered incidentally without any associated symptoms [4].

Pulmonary carcinoid tumors typically follow an indolent course and surgical resection is the primary treatment. Advanced PCs most commonly metastasize to the mediastinal lymph nodes, liver, and bones [5]. Metastasis of PC to skin and subcutaneous tissue is uncommon.

Case Synopsis

The patient is a 71-year-old woman who presented with a 10-month history of two tender nodules on her right mid flank (**Figure 1**). She had a 11-year history of primary atypical and typical PC that was peripherally located. She had undergone multiple unsuccessful surgical resections. A CT scan two months prior to presentation showed increased known mediastinal lymph node metastases and subcutaneous masses (**Figure 2**). She was not a suitable candidate for further surgical intervention given her limited respiratory volume and was

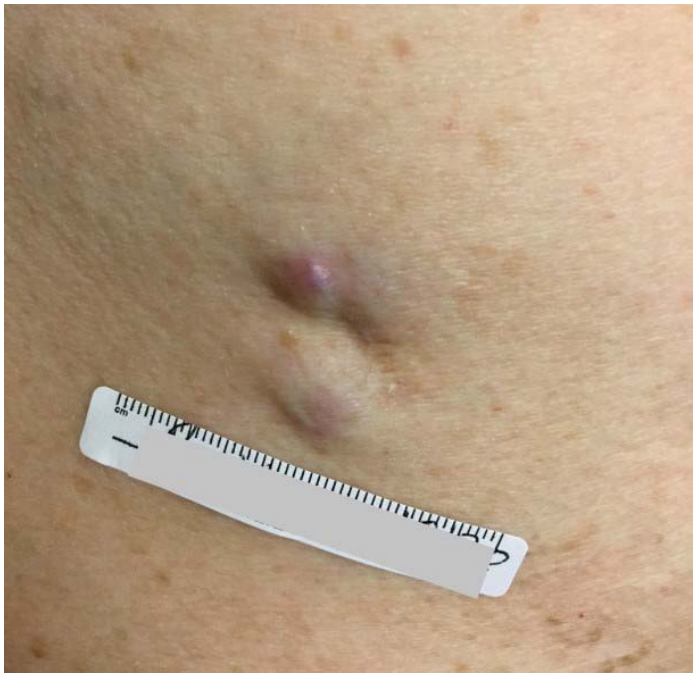

Figure 1. *Two well-defined 6mm×4mm evenly violaceous firm nodules adjacent to a well-healed 2cm surgical scar on the right mid flank.*

managed medically with octreotide infusions. At presentation, she had dyspnea on exertion and required continuous supplemental oxygen. The patient reported a remote history of smoking tobacco.

Physical examination revealed two well-defined 6mm×4mm evenly violaceous firm nodules adjacent to a well-healed 2cm surgical scar from a minimally invasive lobectomy four years prior to presentation (**Figure 1**). No similar lesions were reported by the patient or present on examination.

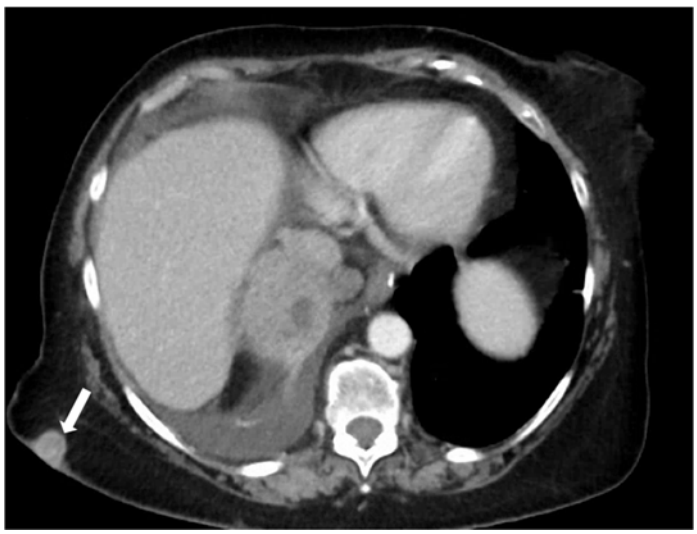

Figure 2. *Abdominal CT scan with intravenous contrast. White arrow showing subcutaneous carcinoid metastasis. A large right pleuro-parenchymal lung mass and small right pleural effusion can also be appreciated.*

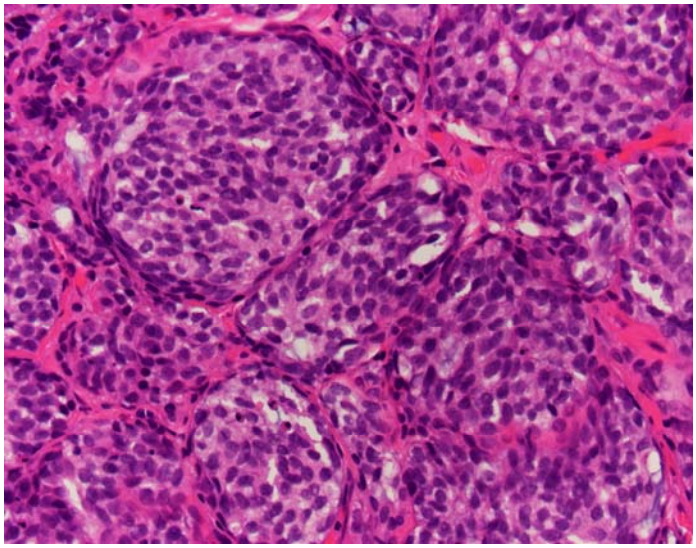

Figure 3. *Evidence of single cell necrosis and fewer than one mitotic figure per 10 high power field. H&E, 100x.*

A punch biopsy from the center of the inferior-most nodule was performed. Histology demonstrated archetypal carcinoid tumor with nested architecture, low mitotic burden of fewer than one mitotic figure per 10 high power fields, and scattered single-cell necrosis (**Figure 3**). Immunohistochemical staining revealed positive staining for chromogranin, synaptophysin, and thyroid transcriptional factor-1 (TTF-1), (**Figure 4**). Given the patient's history of metastatic atypical PC together with the tumor morphology and immunophenotype, a diagnosis of subcutaneous metastatic atypical PC was made. The patient elected to continue with palliative medical and physical therapies.

Case Discussion

Pulmonary carcinoid tumors are uncommon pulmonary neoplasms with an incidence of 0.5-5% of all diagnosed lung cancers [2]. Atypical PCs are an intermediate grade carcinoid tumor representing 10-35% of all PCs [2]. Atypical PCs present a decade later than typical PCs and are associated with tobacco use [6]. Pulmonary carcinoid tumors present most commonly with respiratory symptoms and less

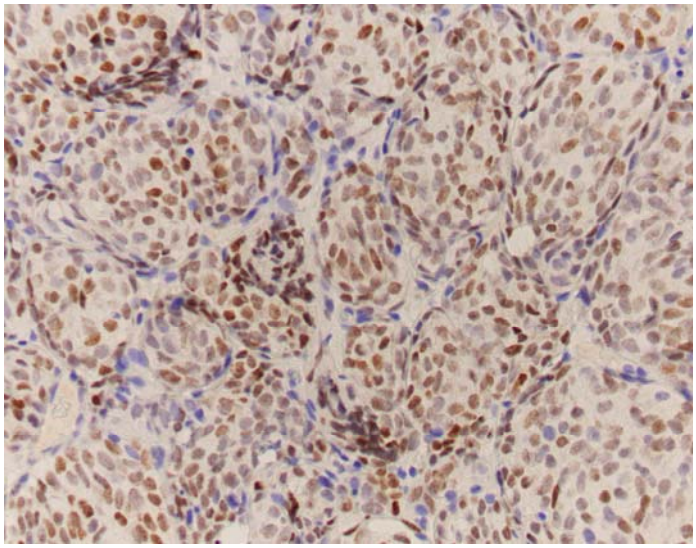

Figure 4. *Immunostaining for thyroid transcriptional factor-1 (TTF-1), 400x. The tumor cells stain positively for TTF-1, a marker of carcinoid tumors of the lung.*

commonly with accompanying serotonergic symptoms. Smaller PCs may be found incidentally. The indolent nature and non-specific symptoms of PCs can contribute to a delayed diagnosis [1]. There are no randomized controlled trials examining the treatment of PCs, but surgical resection is considered the standard of care [2,5,6]. The average 10-year survival rates for typical and atypical PCs range from 82-95% and 30-57%, respectively [2].

Cutaneous metastasis from PCs are uncommon and are limited to case reports in the literature, which describe purple-to-red firm nodules on the trunk and extremities upon presentation [3,7,8]. Associated tenderness, ulceration, and multiplicity are variably reported. The differential diagnosis of a cutaneous neuroendocrine tumor can be comprised of both primary and secondary tumors, including primary cutaneous carcinoid, primary extraskeletal Ewing's sarcoma/primitive neuroectodermal tumor (PNET), and metastasis from a primary neuroendocrine tumor elsewhere, as demonstrated in our case.

There is no standard treatment of cutaneous PC metastases. Their presentation indicates advanced disease. It is unknown whether patients with symptomatic cutaneous metastatic PC may benefit from palliative surgical resection. However, surgical excision has been reported in cases of primary cutaneous neuroendocrine tumors [9]. The presentation of cutaneous metastasis in surgical scar tissue secondary to resection of the primary tumor has been described in cases of colon, breast, and endometrial cancer [10-12]. Lung adenocarcinoma arising in prior surgical and post-traumatic scars have been reported [13]. These reports suggest surgical scar metastasis arise as a result of inoculation of the surgical site by the primary tumor during resection. Our patient's cutaneous PC nodules were located adjacent to a surgical scar from a prior lobectomy. However, no causal link can be established, as existing reports are limited to single cases and case series.

Conclusion

Subcutaneous metastases from carcinoid tumors are rare. Dermatologists should consider metastatic PCs in patients with a history of known carcinoid disease or in those without known carcinoid disease who have hemoptysis or other concerning respiratory symptoms presenting with new, firm violaceous nodules. Histologic determination of PCs is guided by immunostaining for neuroendocrine markers and nuclear markers seen in tumors of pulmonary origin.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol*. 2015;26:1604–20. [PMID: 25646366].
2. Herde RF, Kokeny KE, Reddy CB, et al. Primary Pulmonary Carcinoid Tumor: A Long-term Single Institution Experience. *Am J Clin Oncol*. 2015:1. [PMID: 26270444].
3. Santi R, Massi D, Mazzoni F, Antonuzzo L, Comin CE. Skin metastasis from typical carcinoid tumor of the lung. *J Cutan Pathol*. 2008;35:418–22. [PMID: 18333904].
4. Faten Limaiem, Muhammad Ali Tariq, Jason M. Wallen. Lung Carcinoid Tumors. *NCBI StatPearls*. 2020. [PMID: 30725765].
5. Lim E, Yap YK, De Stavola BL, Nicholson AG, Goldstraw P. The

impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. *J Thorac Cardiovasc Surg*. 2005;130:969–72. [PMID: 16214506].

6. Fink G, Krelbaum T, Yellin A, et al. Pulmonary Carcinoid. *Chest*. 2001;119:1647–51. [PMID: 11399686].
7. Linhas R, Tente D, China N, Conde S, Barroso A. Subcutaneous metastasis of a pulmonary carcinoid tumor: A case report. *Medicine*. 2018;97:e9415. [PMID: 29480829].
8. Pietro Donati, Chiara Panetta, Carlo Cota, Giovanni Paolino, Luca Muscardin. Carcinoid metastasis of the skin appearing as painful tumor. *J Dermatol.* 2013;40:415–6. [PMID: 23414140].
9. Okabayashi A, Nakagawa K, Shimizu N, Tohda-Kinoshita R, Goto K. Case of low-grade neuroendocrine carcinoma of the skin presenting metastases to lymph nodes and peritoneum. *J Dermatol*. 2019;46:720–3. [PMID: 31206216].
10. Alexandrescu D, Vaillant J, Yahr L, Kelemen P, Wiernik P. Unusually large colon cancer cutaneous and subcutaneous metastases occurring in resection scars. *Dermatol Online J*. 2005;11(2):22. [PMID: 16150230].
11. Freund H, Biran S, Laufer N, Eyal Z. Breast cancer arising in surgical scars. *J Surg Oncol*. 1976;8:477–80. [PMID: 994510].
12. Monist M, Lewkowicz D, Jóźwik M, et al. Atypical Endometrial Hyperplasia Arising in a Cesarean Section Scar: A Mechanism of Malignant Transformation. *Case Rep Oncol Med*. 2019;12:317–21. [PMID: 31123458].
13. Ahmed F, Yasin H, Mohamed HE. A Case of Lung Adenocarcinoma Originating from an Old Posttraumatic Scar in a Young Patient. *Case Rep Oncol Med*. 2019;2019:1–3. [PMID: 31093394].