

Collision Tumor versus Multiphenotypic Differentiation: A Case of Carcinoma with Features of Colonic and Lung Primary Tumors

PRADEEP MURTHAIAH¹, ALEXANDER M. TRUSKINOVSKY², SAIRA SHAH² and ARKADIUSZ Z. DUDEK¹

¹Division of Hematology, Oncology and Transplantation, and

²Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, U.S.A.

Abstract. *Background:* Collision tumors are rare tumors composed of two histologically distinct neoplasms coinciding at the same location. Collision tumors need to be distinguished from tumors originating from a progenitor cell with potential for multiphenotypic differentiation. *Case Report:* A clinically puzzling case of an intricate malignant pulmonary nodule in a patient with previous history of colorectal carcinoma is reported. A brief review of the clinical literature on collision tumor and tumor stem cells is presented. *Conclusion:* This case report emphasizes the importance of detailed histopathologic and immunohistochemical analyses, and clinical history in diagnosing a tumor composed of multiple malignant morphologies.

Collision tumors are rare clinical entities wherein two histologically distinct tumor types occur at the same anatomic site. Collision of the two malignancies can occur between tumors originating in the same organ or between metastases from other sites. Examples of collision tumors have been described in multiple locations, including gastric cardia, cervix, urinary bladder, liver, lung, oral cavity, thyroid, ovary and bile duct (1-10). The majority of these tumors represent collisions between carcinomas and sarcomas or lymphomas and rarely between two types of carcinomas. Primary pulmonary collision tumor is extremely rare and its pathogenesis is still obscure. Diagnosing collision tumors is challenging, especially given recent reports that primary tumors may originate from tumor stem cells, which could mimic the multiple cancers in a collision tumor. Here a puzzling case of a complex pulmonary

tumor occurring in a 70-year-old man is reported. This case report emphasizes the importance of detailed histopathologic and immunohistochemical analyses and clinical history along with thoughtful discussion between the clinician and the pathologist in better defining a diagnosis.

Case Report

A 70-year-old Caucasian man was diagnosed with stage IIB non-small cell lung cancer of the left upper lobe in 1999. At that time, he was treated with neoadjuvant chemotherapy consisting of 2 cycles of cisplatin and etoposide followed by radiation therapy consisting of 45 gray. He then underwent lobectomy in March 2000. Over the next seven years, he was monitored with serial computed tomography (CT) scans performed at regular intervals. All of these scans were normal, with the exception of a partially calcified, spiculated right apical pulmonary nodule, which was stable in size. On a CT scan in April 2007, however, the nodule showed an interval increase in size from 9×9 mm to 12×13 mm. In May 2007, he underwent thoracoscopic wedge resection of the right upper lobe nodule.

The resected wedge of lung contained a firm whitish gray nodule measuring 1.8×1.1×1.0 cm, which closely approached the pleura but did not invade it grossly. No angiolympathic invasion was evident. Resection margins were free of tumor. Immunoperoxidase stains were performed for cytokeratin 7, cytokeratin 20, thyroid transcription factor 1 (TTF-1), caudal type homeobox transcription factor 2 (CDX-2), and epidermal growth factor receptor (EGFR). Tissue sections showed moderately differentiated adenocarcinoma with focal squamous differentiation (Figure 1a). The adenocarcinoma showed two architectural patterns. A macroglandular architecture was characterized by small and large glands lined by tall columnar epithelium with hyperchromatic, pseudostratified, atypical nuclei (Figure 1b). A microcystic-to-solid architecture was characterized by cuboidal neoplastic cells (Figure 1c). In one area of the nodule, the two glandular patterns were continuous with each other, even showing both of their respective types of neoplastic epithelium occupying the same gland (Figure 1d).

Correspondence to: Arkadiusz Dudek, MD, Ph.D., Associate Professor of Medicine Division of Hematology, Oncology and Transplantation University of Minnesota, 420 Delaware Street SE, MMC 480 Minneapolis, MN 55455, U.S.A. Tel: +01 612 624 0123, Fax: +01 612 625 6919, e-mail: dudek002@umn.edu

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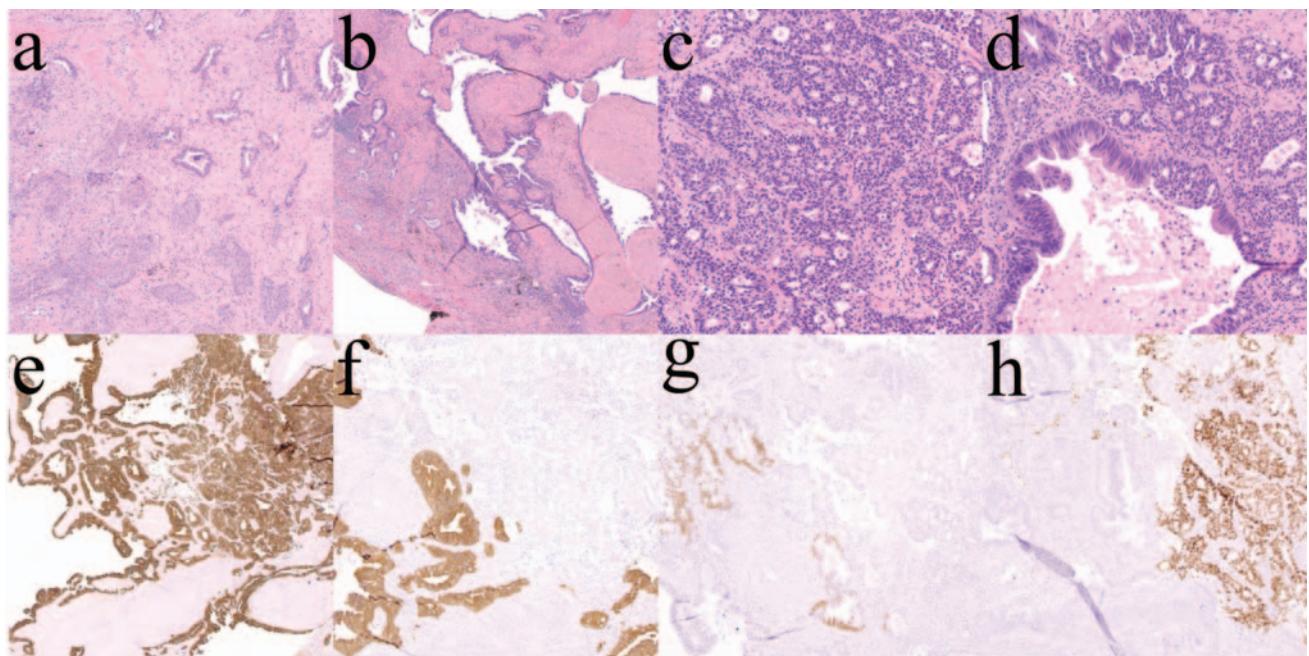


Figure 1. Tissue sections showing moderately differentiated adenocarcinoma with focal squamous differentiation. (a) Macroglandular architecture characterized by small and large glands lined by tall columnar epithelium with hyperchromatic, pseudostratified and atypical nuclei. (b) Microcystic-to-solid architecture with more cuboidal neoplastic cells. (c) Continuous area where the two glandular patterns merge with each other and occupy the same gland. (d) Both architectural patterns of adenocarcinoma were strongly immunoreactive for cytokeratin 7. (e-f) Macroglandular component showed positive immunostaining for cytokeratin 20 (e) and focal positive immunostaining for CDX-2 (f). (g-h) Microglandular adenocarcinoma component showed negative immunostaining for cytokeratin 20 and CDX-2 (g), but was positive for TTF-1 (h).

Immunostaining showed that both architectural patterns of adenocarcinoma were equally strongly immunoreactive for cytokeratin 7 (Figure 1e). Only the macroglandular component showed positive immunostaining for cytokeratin 20 (Figure 1f) and focal positive immunostaining for the intestinal marker CDX-2 (Figure 1g). In contrast, only the microglandular adenocarcinoma component was positive for the pulmonary and thyroid marker TTF-1 (Figure 1h). Both tumor components were positive for epidermal growth factor receptor.

The patient reported a history of colon cancer diagnosed and treated with partial colectomy 20 years ago. Since then, follow-up colonoscopic examinations performed at regular intervals were normal, with no sign of cancer recurrence. Colonoscopies performed a year prior to and shortly after resection of the pulmonary nodule showed no evidence of abnormality within the colon. Based on the long-term absence of colorectal carcinoma and inconclusive immunostaining evidence, a diagnosis was reached favoring the hypothesis that the resected tumor consisted of primary lung cancer with triphenotypic differentiation. The physician discussed the treatment options with the patient including adjuvant chemotherapy for stage IA lung cancer and systemic therapy for metastatic colorectal carcinoma. A decision was made to perform follow-up CT scans at 3 month intervals without additional systemic therapy.

After 24 months of follow-up, there was no evidence of cancer recurrence. The patient continues to be monitored with physical examinations and imaging scans.

Discussion

One possible explanation for the complex morphologic findings in the resected pulmonary tumor is that this carcinoma was capable of producing several lines of differentiation, including glandular and squamous. Among the glandular component, there were two distinct, although continuous, patterns. Morphologically, the macroglandular pattern resembled colorectal adenocarcinoma with evidence of intestinal differentiation as demonstrated by positive immunoreactivity for cytokeratin 20 and CDX-2. However, the macroglandular pattern was also strongly and diffusely positive for cytokeratin 7, as was the microglandular component, which had a more typical pulmonary immunohistochemical profile, including negative immunostaining for cytokeratin 20 and positive immunostaining for TTF-1.

Another possible explanation for this intricate pathologic appearance was that the tumor was a collision of two histologically distinct tumor types, with metastatic colorectal cancer growing inside of a pulmonary malignancy. The

coexistence of two or more primary tumors is relatively rare. Some of the hypotheses put forward to explain the rare phenomenon of collision tumor are: 1) The occurrence is coincidental, especially in tumors originating from neighboring tissues (9, 11); 2) A carcinogenic agent may interact with different tissues, inducing different tumors (9, 11), or; 3) An oncogenic growth factor produced by a metastatic tumor that could induce the growth of primary cancer at the site of metastases or may favor the differentiation of metastatic lesion to mimic the histology of primary tumor from the organ of metastatic lesion (12,13); and finally 4) Alteration in the microenvironment, such as angiogenesis and inflammation, by the primary tumor could facilitate the growth of metastases from a second primary tumor from another organ (13, 16).

Collision tumors should be differentiated from composed, or mixed, tumors. Mixed tumors are formed by more than one type of neoplastic tissue with histological characteristics of different primary tumors. However, they have the same histological origin, as shown by transition areas (14, 15). A diagnosis of collision tumor also needs to rule out the intensely debated tumor stem cell hypothesis (17). According to this hypothesis, tumors originate from the tissue stem cells of the primary organ, which through mutations evade the tightly regulated process of self-renewal. Mutated tissue stem cells then generate a differentiated progeny of cells which, uncontrolled by physiologic signals, are allowed to proliferate and form tumors. In this clinical case, the existence of bronchoalveolar stem cells (18) could differentiate into different histologies and explain the confusing presence of three different malignant morphologies in one tumor.

The diverse morphology of the tumor described in this case leads to a clinical dilemma. If one were to conclude that the findings are consistent with a diagnosis of collision of stage IA lung primary with metastatic colorectal carcinoma, then the most optimal therapy for this patient would include systemic chemotherapy for metastatic colorectal carcinoma. However, the long interval from the diagnosis of colorectal carcinoma (20 years) and a careful consideration of the possibility of a primary lung tumor (lung cancer stem cell) differentiating into three distinct histologies (squamous, macrograndular and microcystic adenocarcinomas) led to the diagnosis of stage IA non-small cell lung cancer. As a result, no further therapy was required, only follow-up monitoring. Had the patient history included a more recent occurrence of colorectal carcinoma, however, the patient very likely would have been treated with additional systemic therapy.

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