

Case Report

Pagetoid involvement of bronchioles by metastatic breast carcinoma

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Summary

We report a case of a 36-year-old female with endobronchiolar spread of breast carcinoma in the lung. The patient had recently been diagnosed with invasive ductal breast carcinoma and imaging of the lungs revealed bilateral lung nodules. She then underwent a wedge resection of a lung nodule. The biopsy revealed a subpleural metastatic nodule of invasive ductal carcinoma with an intra-alveolar pattern of spread at its advancing edge. Several smaller foci of intra-alveolar tumor were noted as well as pagetoid spread of tumor cells along a 0.9 mm wide bronchiole. The neoplastic cells were TTF-1 negative, GATA3 positive and ER positive. This is the third reported case of pagetoid spread of metastatic breast carcinoma along the bronchial tree. This case emphasizes the importance of examining not only bronchi but also bronchioles to detect this unusual pattern of spread of metastatic breast carcinoma in lung resection specimens.

Key words: endobronchiolar pagetoid spread, metastatic breast cancer, lung metastasis

Introduction

Mammary and extramammary Paget's disease both indicate the spread of carcinoma cells along epidermal skin surfaces. Pagetoid spread is a term applied to the spread of tumor cells along mucosal or glandular surfaces such as mammary ducts, urothelium, or bronchial mucosa. Even though the Armed Forces Institute of Pathology (AFIP) fascicle *Tumors of the Lower Respiratory Tract* from 1994 stated that "pagetoid spread of carcinoma cells in the small and large airways is an occasional incidental histologic finding," there are only a few reports documenting pagetoid spread of lung cancer along bronchial mucosa, and even fewer reports of metastatic tumors to the lung showing this same pattern of spread¹. We discuss the findings in a case of metastatic breast carcinoma to the lung with pagetoid spread along the bronchiolar mucosal surface.

Case report

A 36-year-old female initially presented with a right breast mass that revealed invasive ductal carcinoma on core biopsy. Her breast tumor was estrogen receptor (ER)-positive, progesterone receptor (PR)-negative, HER2-equivocal on immunohistochemistry (IHC) and HER2-negative by fluorescence in situ hybridization (FISH). Additional work-up revealed bilateral pulmonary nodules. She thus underwent a video-assisted thoracoscopic surgical wedge resection of a peripheral subpleural left lung nodule.

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Conflict of interest

The Authors declare no conflict of interest.

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Pathologic findings

The specimen consisted of a 4.0 gm wedge of lung tissue measuring 6 x 2 x 2 cm. A 1.0 x 0.9 x 0.8 cm firm subpleural nodule was noted. Microscopic examination of the nodule revealed invasive carcinoma with a desmoplastic stromal reaction (Fig. 1A). At the interface with the surrounding lung parenchyma, the tumor cells invaded the airspaces leaving the alveolar wall framework intact. A separate focus of tumor was identified and was ascribed to “spread through the air spaces” (STAS) pattern of invasion (Figs. 1B, 1C). At 5 mm from this focus of tumor and 9 mm from the subpleural tumor nodule, a bronchiole measuring 0.9 mm in diameter revealed atypical epithelial cells situated above the basement membrane within the epithelium of the bronchiolar mucosa (Figs. 1B, 1D). The atypical cells had large round nuclei with a central prominent nucleolus (Fig. 2A). These cells were positive for ER and GATA-binding protein 3 (GATA-3), and negative for thyroid transcription factor-1 (TTF-1), thus confirming their mammary origin (Figs. 2B-2D). The tumor cells also showed membrane staining for HER2 (2+), but the overall metastasis was HER2-negative by FISH. With the knowledge of pagetoid involvement by tumor cells in this bronchiole, the remaining histologic sections, including those from the resection margin, were carefully reviewed and no additional foci of endobronchial pagetoid spread were identified.

Discussion

Endobronchial metastases, defined as primary involvement of the bronchial mucosa by non-pulmonary tumors, are uncommon and originate mainly from the breast, colorectum and kidney. Possible routes involved in endobronchial spread include hematogenous, lymphatic, aerogenous, and direct invasion from an adjacent tumor in the lung parenchyma, mediastinum or regional lymph nodes. These metastases have been classified into 4 types by Kiryu et al: *type I* represents a direct metastasis to the bronchus; *type II* is bronchial invasion by a parenchymal lesion; *type III* is bronchial involvement by a mediastinal or hilar lymph node metastasis; and *type IV* represents a peripheral lesion extending from the proximal bronchus². The frequency of endobronchial metastases varies from 2 to 50% according to which type of metastatic pattern is included. Primary (type I) endobronchial metastases are the least frequent, while secondary lesions (types II-IV) are more frequent.

Pagetoid spread along the bronchial mucosa has been more often described as a process involving

primary lung cancers. Such an occurrence has been reported in small and large cell neuroendocrine carcinomas, undifferentiated carcinomas, and adenocarcinomas of the lung. The first report was in 1956 when Cooper and Totten described pagetoid spread of undifferentiated lung carcinoma cells within the bronchial epithelium of the mainstem and lobar bronchi³. Other authors have described or depicted pagetoid spread of a variety of lung carcinomas along bronchi or bronchioles⁴⁻⁸.

Endobronchial pagetoid spread of non-pulmonary tumors, on the other hand, is extremely rare. One patient with cutaneous sebaceous carcinoma developed bronchial metastasis in which pagetoid spread of neoplastic cells was noted only along the ducts of the bronchial seromucinous glands⁹. Another patient developed metastatic melanoma to the lung 7 years after removal of a primary cutaneous melanoma of the back. The lung demonstrated pagetoid spread of S100-positive melanoma cells in many small bronchi and bronchioles¹⁰. In addition, two cases of endobronchial breast carcinoma metastases with pagetoid histology have been documented. In 2011, West et al described a patient who developed a lung metastasis 9 years after a diagnosis of invasive ductal breast carcinoma. During the next 5 years she developed additional lung metastases as well as friable and erythematous bronchial mucosa seen on bronchoscopic examination. An endobronchial biopsy of the mainstem bronchus revealed pagetoid intraepithelial spread of metastatic breast carcinoma cells¹¹. In 2017, Monica et al. reported a case of a patient with a lung nodule 6 years after resection of an invasive breast carcinoma. A wedge lung resection revealed a nodule of metastatic breast carcinoma as well as endobronchial pagetoid involvement of a bronchus at the resection margin¹². In both cases, IHC was useful in confirming the diagnosis (Tab. I). It is intriguing that, similar to Paget's disease of the nipple, the few documented cases of endobronchial spread have been involved by the ductal variant of breast carcinoma, while it is known that within the breast it is the lobular type that shows a greater propensity for pagetoid spread along ducts.

The differential diagnosis of endobronchial pagetoid intraepithelial lesions includes a variety of tumors that may display a pagetoid pattern of spread, such as primary lung carcinomas, metastasis of extrapulmonary neoplasms (breast, melanoma, etc.), and primary squamous carcinoma in situ of the bronchus. Any dilemma may be resolved by the use of organ-specific immunohistochemical stains such as TTF-1 for lung, ER, PR, and GATA3 for breast, S100 and melan-A for melanoma, and high molecular weight keratin, p40 or p63 for squamous carcinoma. The selection of

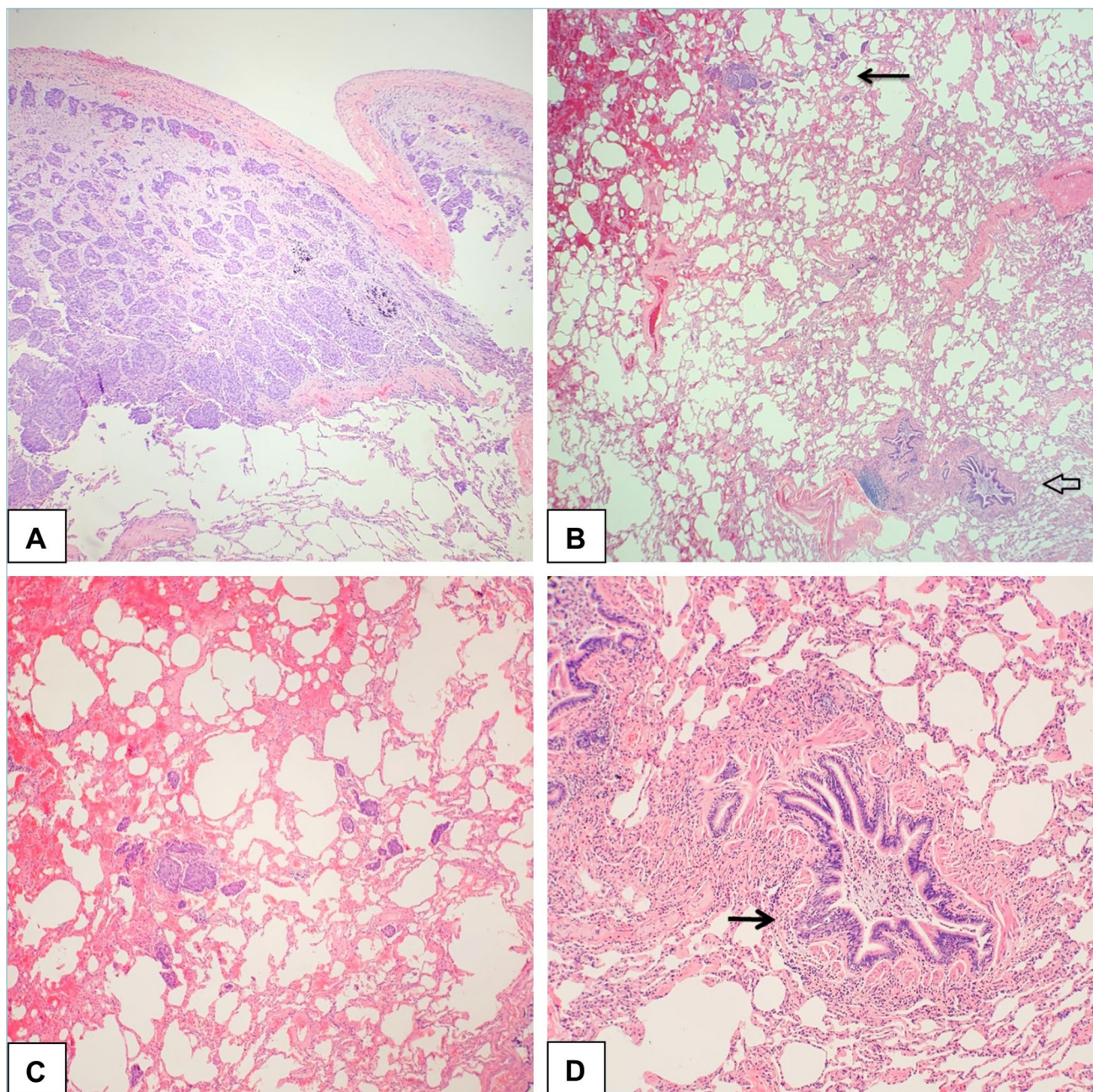


Figure 1. (A) Subpleural nodule of metastatic breast carcinoma (H&E, 40x). (B) Low-power histological section of lung showing metastatic breast carcinoma involving air spaces (arrow) and a bronchiole involved by pagetoid spread (open arrow). The main subpleural metastatic lesion (not included) is present at 9 mm from this bronchiole (H&E, 20x). (C) Focus of tumor showing spread through air spaces (STAS) pattern of invasion (H&E, 40x). (D) Bronchiole with pagetoid involvement by tumor cells which on low power examination revealed subtle changes such as pallor and slight thickening of the bronchiolar mucosa (arrow) (H&E, 40x).

Table I. Reported cases of endobronchial pagetoid spread of metastatic breast carcinoma.

Reference	Age	Breast cancer diagnosis	Lung operation	Site of bronchial involvement	Positive IHC markers	Negative IHC markers
West et al. (2011) ¹¹	56	IDC	Wedge	Mainstem bronchus	ER, PR, HER2, CAM5.2	TTF-1, 34βE12
Monica et al. (2017) ¹²	73	IDC	Wedge	“Large bronchus”	ER, HER2, AR, GCDFFP-15	TTF-1
current case	36	IDC	Wedge	Bronchiole	ER, GATA3, HER2	TTF-1

IDC = invasive ductal carcinoma; IHC = immunohistochemistry; ER = estrogen receptor; PR = progesterone receptor; AR = androgen receptor; CAM5.2 = low molecular weight cytokeratin CK7/8; 34βE12 = high molecular weight cytokeratin (CK903); GCDFFP-15 = gross cystic disease fluid protein-15; TTF-1 = thyroid transcription factor-1.

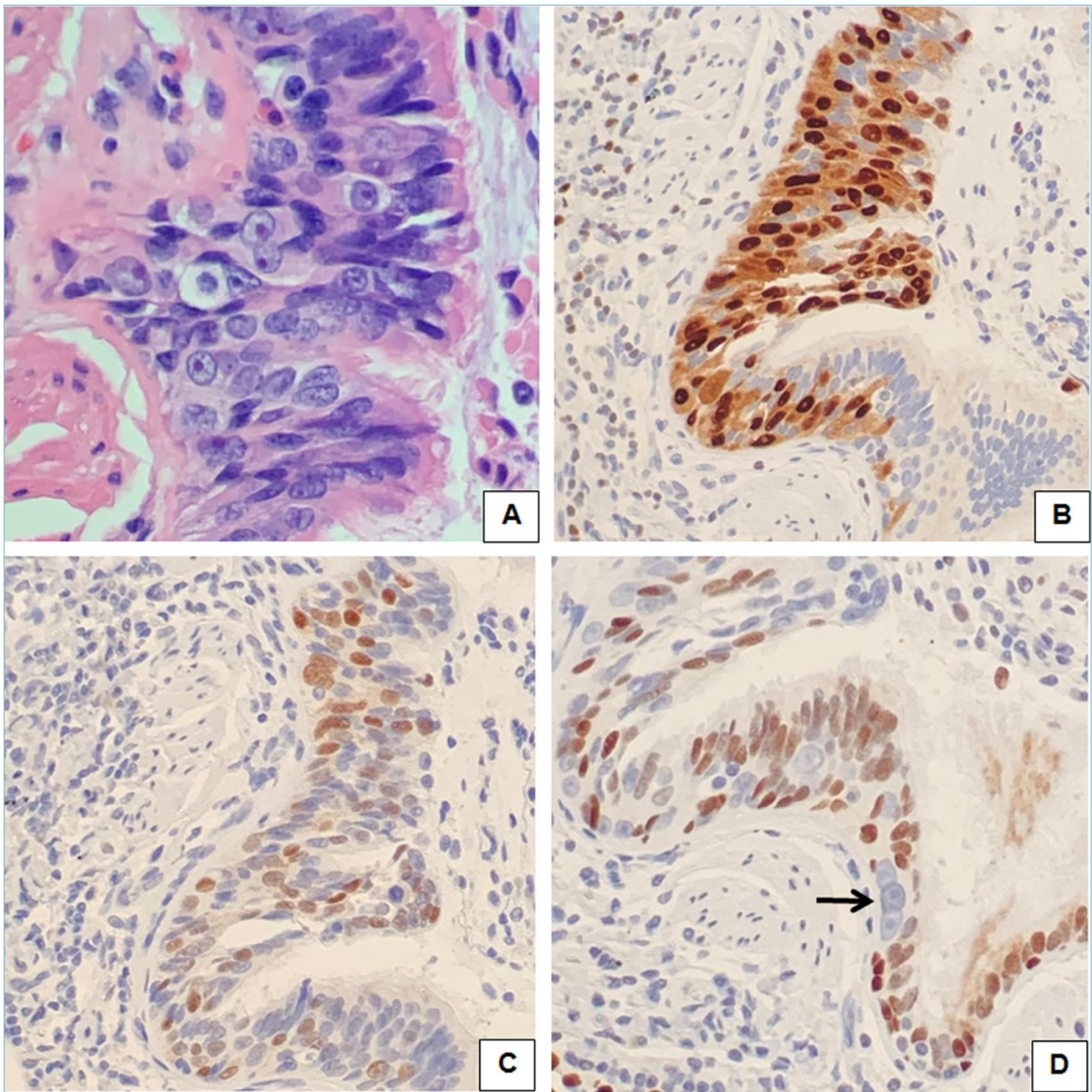


Figure 2. Bronchiole with pagetoid spread of metastatic breast carcinoma. (A) Bronchiolar wall with malignant epithelial cells within the ciliated epithelial layer. The tumor cells show large round nuclei with a prominent central nucleolus. (H&E, 400 x). (B) GATA3 immunostain highlights the nuclei of the breast carcinoma cells within the bronchiolar mucosa. (C) ER immunostain is positive in the nuclei of the metastatic breast carcinoma cells. (D) TTF-1 strongly stains the nuclei of bronchiolar basal cells, and less intensely some of the ciliated epithelial cells. The large nucleolated breast tumor cells are negative for TTF-1 (arrow).

the IHC stain must be tailored to the appearance of the bronchial mucosa (i.e., with or without squamous metaplasia) and is distinct from that recommended for Paget's disease of the skin since certain immunos-

tains, such as CK7 and EMA which are advocated to highlight Paget cells in skin, will also stain normal bronchial epithelium (Tab. II).

Our case exemplifies the unusual possibility that met-

Table II. Differential diagnosis of endobronchial pagetoid spread of breast carcinoma: immunohistochemical stains.

Diagnosis	CK7	CK20	EMA	CAM5.2	p40	p63	ER/PR	HER2	GATA3	CK903	CK5/6	TTF-1	Mel
Bronchial pagetoid breast carcinoma	+	-	+	+	-	-	+/- ^a	+/- ^a	+	-	-	-	-
Bronchial pagetoid lung adenocarcinoma	+	-/+ ^b	+	+	-	-	-	-	-	-	-	+	-
Bronchial pagetoid malignant melanoma	-	-	-	-	-	-	-	-	-	-	-	-	+
SCCIS	-	-	-	-	+	+	-	-	-	+	+	-	-
Normal bronchus	+	-	+	+	-/+ ^c	-/+ ^c	-	-	-	-	-	+	-
Squamous metaplasia of bronchus	-	-	-	-	+	+	-	-	-	+	+	-	-
Paget's of skin	+	-/+ ^d	+	+	-	-	+/- ^a	+/- ^a	+	-	-	-	-

EMA = epithelial membrane antigen; Mel = melanocytic markers (S100, melan-A, HMB45); SCCIS = squamous cell carcinoma in-situ; a = ER/PR/HER2 depend on status of the primary breast tumor; b = mucinous carcinoma may be CK20+ and TTF-1 negative; c = normal basal cells are p40/p63+; d = secondary extramammary Paget disease from rectum or urothelium is CK20+.

astatic breast carcinoma to the lung may demonstrate pagetoid involvement of the bronchial tree. This subtle pattern of spread can be easily overlooked and its recognition is most important when evaluating the resection margin of a lung specimen. Its presence may complicate any attempt to obtain a complete surgical resection, especially in the case of a solitary lung nodule. From the few cases reported, it is clear that this pagetoid pattern of spread of metastatic breast carcinoma may occur anywhere along the entire length of the bronchial tree.

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