Giant Secondary Overgrowth of Type-1 Pulmonary Cystic Airway Malformation Upon Development of Anaplastic Lymphoma Kinase–Rearranged Adenocarcinoma

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We herein report on a giant secondary overgrowth of type-1 pulmonary cystic airway malformation (PCAM) occurring upon development of ALK receptor tyrosine kinase (*ALK*)–rearranged adenocarcinoma as documented from imaging, pathology, immunohistochemistry, and fluorescence in situ hybridization (FISH) for *ALK*. PCAMs, formerly known as congenital cystic adenomatoid malformations, are the most frequent cystic malformations in the lung, with five different subtypes (from the type 0 to the type 4) being classified according to the presumed site of malformed growth within the tracheobronchial tree (from a proximal one involving the trachea to a distal one affecting the acinar spaces).[1,2] Either segmental and temporary interruption of the tracheobronchial tree due to unbalanced interaction of epithelial and mesenchymal anlages or functional/organic airway obstruction during organogenesis has been tentatively advocated in the pathogenesis of PCAMs, although ultimate mechanisms remain elusive.[1] Type 1 accounts for more than 50% of PCAM instances, unilaterally affects lungs without further malformations, and occurs in adults, especially males, as incidental findings or recurrent infections.[1-3] Type 1 PCAM is deemed to arise from dilation of distal bronchi or proximal bronchioles resulting in single to few clustered cysts, which have pulmonary vessels and size up to 10 cm in diameter and histologically features components of the bronchial wall, such as respiratory columnar cells, smooth muscle layers, nerves, fibrous tissue, and/or hyaline cartilage islets.[1-4] Type 1 PCAM can also harbor hyperplastic or neoplastic lesions, either dysplastic/pre-invasive, or frankly invasive, which comprises mucous cell hyperplasia, intracystic/extracystic mucinous cell proliferation, mucinogenic growth, non-mucinous atypical adenomatous hyperplasia, atypical goblet cell hyperplasia, adenocarcinoma of either mucinous and non-mucinous types, squamous cell carcinoma, bronchial carcinoid, and mucoepidermoid carcinoma.[4-12] Chromosomal aberrations, *KRAS* proto-oncogene and EGFR mutations and *ALK* gene translocation have been described in type 1 PCAM in both neoplastic and atypical but not normal lung tissue supporting some pathogenetic roles.[5,7-11] Among adenocarcinomas with *ALK* rearrangement, solid/semisolid/ground glass opacities are usually documented, whereas cystic configuration is decidedly uncommon, thus making an inherent propensity of these tumors to cyst

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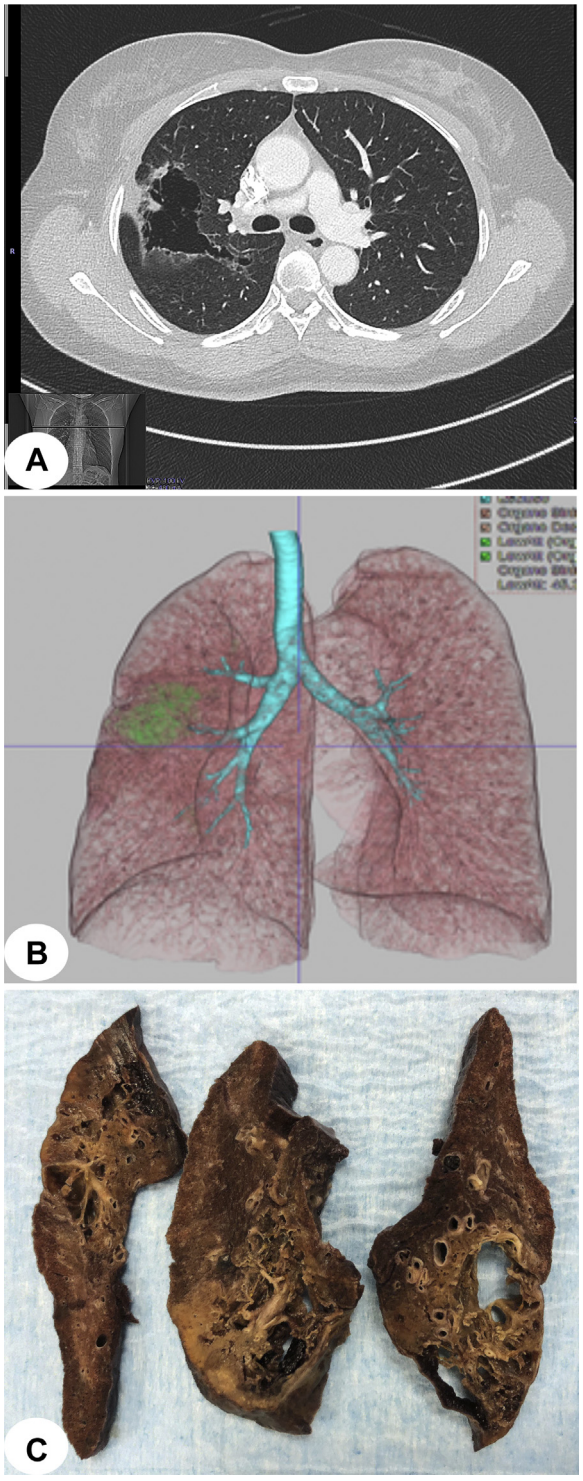

Figure 1. Computed tomography scan examination revealed a large cystic lesion with infiltrated margins of the right upper and middle lobes (*A*). Three-dimensional reconstruction confirmed a cystic lesion abutting the visceral pleura (*B*). Gross preparation of the lung showed an irregular, anfractuous and multilocular cyst with margin infiltration but predominant dilation due to air trapping (*C*).

evolution unlikely.[13,14] Although full-fledged type 1 PCAMs most often antecede, sometimes by years, the subsequent development of lung cancer, the opposite (i.e., secondary giant secondary overgrowths of small and undeveloped/undisclosed cysts upon an ALK-rearranged adenocarcinoma) was unprecedented.[9-11]

Briefly, a 42-year-old Chinese female nonsmoker with an unremarkable clinical history was admitted to hospital because of sudden appearance of hemoptysis due to a 6-cm–sized, air-trapping cyst involving the upper and middle right lobes. There were irregular and slightly infiltrated cystic edges which abutted thickened visceral pleura and presented with hilar/mediastinal lymph node involvement. No signs of emphysema, interstitial lung disease, bronchiectasis, pleural effusion, or distant metastases were seen at the time of diagnosis (Figs. 1 *A* and *B*). Laboratory and clinical findings were unremarkable for vasculitis or autoimmune diseases. Bronchoscopy was negative, whereas bronchial aspirate and lavage fluids pushed micropapillary neoplastic aggregates consistent with adenocarcinoma to appear (Fig, 2*A*, *inset*). The patient thus underwent right bi-lobectomy with extended mediastinal lymph node excision, which revealed a multilocular and anfractuous cystic lesion with pushing and infiltrated edges (Fig. 1*C*). Microscopically, an adenocarcinoma with acinar (40%), papillary (30%), micropapillary (25%), and lepidic (5%) patterns of growth was documented (Fig. 2*A*, *main picture*), with tumor cells covering the entire internal surface of the cystic wall, with no recognizable residual bronchial/alveolar respiratory epithelium (Figs. 2*B* and *C*). Cyst wall instead included remnants of the bronchial wall, such as respiratory epithelium (Figs. 2*B*, 2*C*, and 2*D*), even with goblet cell metaplasia (Fig. 2*B*, *), nerve fibers along with hyaline cartilage islets (Fig. 2*B*, *short arrow*), and disarrayed smooth muscle layers beneath the cystic neoplastic epithelium (Figs. 2*C* and *D*, *short arrows*). The latter was also highlighted by desmin decoration (clone DE-R-11, Ventana-F. Hoffmann-La Roche Ltd., Basel, Switzerland) immunoreactivity (Fig. 2*D*, *inset*). Immunostaining for ALK protein (clone D5F3, Ventana ALK CDx Assay on BenchMark ULTRA automated staining instrument, F. Hoffmann-La Roche Ltd.) revealed strong and diffuse reactivity (Fig. 2*E*), along with transcription termination factor 1 (TTF1) nuclear (clone 8G7G3/1, Ventana-Roche) decoration (Fig. 2*E*, *inset*). A final diagnosis of lung adenocarcinoma arising within a type 1 PCAM was rendered, staged pT3N2 (IIIB, according to Union for International Cancer Control/American Joint Committee on Cancer criteria, eighth edition) because of one hilar N1 and one paratracheal N2 metastatic lymph

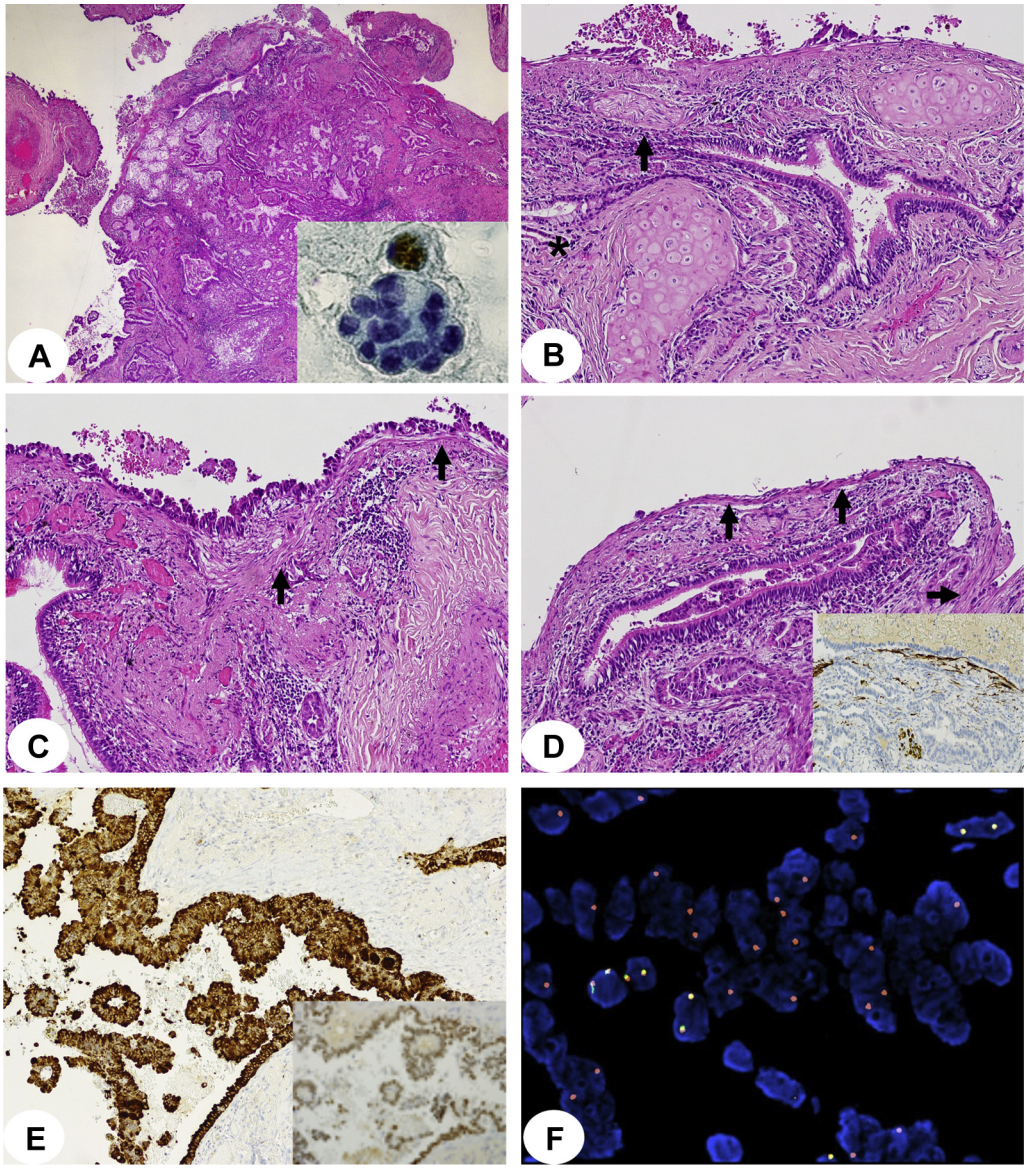

Figure 2. Cytologic examination of bronchial fluids showed micropapillary aggregates of adenocarcinoma cells (*A, inset*), which were seen to infiltrate the cystic edges (*A, main picture*) with residual bronchioles (*B, upper part*) but not normal bronchial/alveolar epithelium layering the cystic surface (*B,C*). However, remnants of respiratory epithelium (*B* to *D*), sometimes with goblet cell metaplasia (*B*, *), nerve fibers (*B, short arrow*), and disarrayed layers of smooth muscle (*C,D,* even upon desmin decoration as an *inset* in *D*) was observed beneath the neoplastic epithelium reinforcing once again the diagnosis of type 1 pulmonary cystic airway malformation. Immunohistochemistry for ALK protein revealed a diffuse and intense decoration in all tumor cells (*E*), along with thyroid transcription factor-1 (*E, inset*). Fluorescence in situ hybridization analysis by means of dual color break-apart kit showed splitting red signals along with fusion yellow signals, indicative of *ALK* translocation (*F*).

node. Because of its impressive ALK protein positivity, a FISH confirmation for *ALK* translocation was performed by means of a commercially available dual-color break apart probe kit (Vysis ALK Break Apart FISH CE-IVD, Abbott Laboratories, Lake Bluff, Illinois) showing splitting red signals along with fusion signals (Fig. 2*F*). The patient underwent four cycles of adjuvant chemotherapy with cisplatin and paclitaxel and currently is alive and well with no signs of recurrent disease after 8-month follow-up. Mechanically, check valve mechanisms were likely to be responsible for such a giant secondary cystic overgrowth from small and undeveloped/undisclosed cysts via distal airway obstruction, inasmuch as parenchymal air-trapping dilation by far prevailed over solid margination by growing tumor cells.[15,16]

The presence of disarrayed elements of bronchial origin in the cyst wall, along with clinical and laboratory findings and the lack of additional imaging alterations were all in keeping with an ALK-positive ADC- arising in type 1 PCAM and allowed other congenital or acquired

cystic changes of the lung, either neoplastic or non-neoplastic, to be consistently ruled out (e.g., bronchiectasis, intra-lobar sequestration, mesenchymal cystic hamartoma, bronchogenic cyst, thin-walled emphysematous cyst, parenchymal cystic remodeling by perivascular epithelioid cells in lymphangioleiomyomatosis, tuberculosis and other fibro-inflammatory cysts, interstitial lung disease, vasculitis, and common lung cancer cavitation).[1,15-18] Re-evaluation of two unrelated chest radiographs dating back to 9 and 5 years before failed to show any recognizable cyst in the same anatomical region of the right lung, confirming a giant secondary overgrowth of a small-sized type 1 PCAM. To this regard, the issue of lung cancer arising within pre-existing cysts or developing along with cyst-forming parenchymal structural changes is clinically emerging especially when dealing with early lung cancer screening action projects.[17] Therefore, multidisciplinary teaming and an accurate workup of pathology and molecular findings are needed to interpret these lesions to offer patients the best therapy options.

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References

1. Leblanc C, Baron M, Desselas E, et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. *Eur J Pediatr*. 2017;176:1559–1571.
2. Stocker J. Congenital pulmonary airway malformation: a new name and an expanded classification of congenital cystic adenomatoid malformations of the lung. *Histopathology*. 2002;41:424–431.
3. Sfakianaki AK, Copel JA. Congenital cystic lesions of the lung: congenital cystic adenomatoid malformation and bronchopulmonary sequestration. *Rev Obstet Gynecol*. 2012;5:85–93.
4. MacSweeney F, Papagiannopoulos K, Goldstraw P, et al. An assessment of the expanded classification of congenital cystic adenomatoid malformations and their relationship to malignant transformation. *Am J Surg Pathol*. 2003;27:1139–1146.
5. Lantuejoul S, Nicholson AG, Sartori G, et al. Mucinous cells in type 1 pulmonary congenital cystic adenomatoid malformation as mucinous bronchioloalveolar carcinoma precursors. *Am J Surg Pathol*. 2007;31:961–969.
6. Rossi G, Gasser B, Sartori G, et al. MUC5AC, cytokeratin 20 and HER2 expression and K-RAS mutations within mucinogenic growth in congenital pulmonary airway malformations. *Histopathology*. 2012;60:1133–1143.
7. Stacher E, Ullmann R, Halbwedl I, et al. Atypical goblet cell hyperplasia in congenital cystic adenomatoid malformation as a possible preneoplasia for pulmonary adenocarcinoma in childhood: a genetic analysis. *Hum Pathol*. 2004;35:565–570.
8. Casagrande A, Pederiva F. Association between congenital lung malformations and lung tumors in children and adults: a systematic review. *J Thorac Oncol*. 2016;11:1837–1845.
9. Hasegawa M, Sakai F, Arimura K, et al. EGFR mutation of adenocarcinoma in congenital cystic adenomatoid malformation/congenital pulmonary airway malformation: a case report. *Jpn J Clin Oncol*. 2014;44:278–281.
10. Kim MY, Kang CH, Park SH. Multifocal synchronous mucinous adenocarcinomas arising in congenital pulmonary airway malformation: a case report with molecular study. *Histopathology*. 2014;65:926–932.
11. Tetsumoto S, Kijima T, Morii E, et al. Echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) rearrangement in congenital pulmonary airway malformation. *Clin Lung Cancer*. 2013;14:457–460.
12. Harini N, Chakravarthy R, Archana L. Congenital pulmonary airway malformation with mucoepidermoid carcinoma: a case report and review of literature. *Indian J Pathol Microbiol*. 2012;55:540–542.
13. Kim TJ, Lee CT, Jheon SH, et al. Radiologic characteristics of surgically resected non-small cell lung cancer with ALK rearrangement or EGFR mutations. *Ann Thorac Surg*. 2016;101:473–480.
14. Nakada T, Okumura S, Kuroda H, et al. Imaging characteristics in ALK fusion-positive lung adenocarcinomas by using HRCT. *Ann Thorac Cardiovasc Surg*. 2015;21:102–108.
15. Deng H, Zhang J, Zhao S, et al. Thin-wall cystic lung cancer: a study of 45 cases. *Oncol Lett*. 2018;16:755–760.
16. Mascalchi M, Attina D, Bertelli E, et al. Lung cancer associated with cystic airspaces. *J Comput Assist Tomogr*. 2015;39:102–108.
17. Farooqi AO, Cham M, Zhang L, et al. Lung cancer associated with cystic airspaces. *AJR Am J Roentgenol*. 2012;199:781–786.
18. Mets OM, Schaefer-Prokop CM, de Jong PA. Cyst-related primary lung malignancies: an important and relatively unknown imaging appearance of (early) lung cancer. *Eur Respir Rev*. 2018;27:pii180079.