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Mucinous adenocarcinoma arising in congenital pulmonary airway malformation: clinicopathological analysis of 37 cases

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Aims: Mucinous adenocarcinoma arising in congenital pulmonary airway malformation (CPAM) is a rare complication, with little being known about its natural course. The aims of this article are to describe a series of mucinous adenocarcinomas arising from CPAMs, and present their clinicopathological features, genetics, and clinical outcome.

Methods and results: Thirty-seven cases were collected within a 34-year period, and the subtype of adenocarcinoma and CPAM, tumour location, stage, growth patterns, molecular data and follow-up were recorded. The cohort comprised CPAM type 1 ($n = 33$) and CPAM type 2 ($n = 4$). Morphologically, 34 cases were mucinous adenocarcinomas (21 *in situ*; 13 invasive), and three were mixed mucinous and non-mucinous adenocarcinoma. Seventeen cases

showed purely extracystic (intra-alveolar) adenocarcinoma, 15 were mixed intracystic and extracystic, and five showed purely intracystic proliferation. Genetically, nine of 10 cases tested positive for KRAS mutations, four with exon 2 G12V mutation and five with exon 2 G12D mutation. Residual disease on completion lobectomy was observed in two cases, and three cases recurred 7, 15 and 32 years after the original diagnosis. Two patients died of metastatic invasive mucinous adenocarcinoma.

Conclusions: Most adenocarcinoma that arise in type 1 CPAMs, are purely mucinous, and are early-stage disease. Intracystic proliferation is associated with lepidic growth, an absence of invasion, and indolent behaviour, whereas extracystic proliferation may be associated with more aggressive behaviour and

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advanced stage. Most cases are cured by lobectomy, and recurrence/residual disease seems to be

associated with limited surgery. Long-term follow-up is needed, as recurrence can occur decades later.

Keywords: adenocarcinoma, congenital pulmonary airway malformation, *KRAS*, mucinous, prognosis

Introduction

Congenital pulmonary airway malformation (CPAM) is a rare cystic lesion composed of architecturally disordered respiratory structures, with the latest reported incidence being 1/2500.¹ Stocker originally described three histological subtypes²; the number of subtypes was later expanded to five,³ although type 0 CPAM is more commonly accepted as acinar dysplasia, and type 4 CPAMs are now viewed as regressed pleuropulmonary blastomas by some.⁴ Type 2 CPAMs are the most common,⁵ and are composed of bronchiole-like cysts <20 mm in cyst size surrounded by underdeveloped/simplified alveolar parenchyma. They are often associated with pulmonary sequestrations.^{5,6} Type 1 CPAMs are rarer, and are composed of one or more cysts >20 mm in diameter, accompanied by smaller cysts and alveolar parenchyma similar to that in type 2 CPAMs.

A proliferation of cytologically bland mucinous cells within the cyst lining is observed in approximately one-third of cases,³ mostly in type 1 CPAMs, but also rarely in type 2 and 3 CPAMs.^{5,7} These lesions have historically been classified as goblet or mucous cell hyperplasia,⁸ mucinous epithelial proliferation,⁹ mucinous metaplasia,¹⁰ and atypical goblet cell hyperplasia (AGCH).^{7,11,12} Occasionally, the mucinous cells also grow along the alveolar septa into the adjacent, sometimes underdeveloped, alveoli; this is microscopically indistinguishable from mucinous adenocarcinoma *in situ* (AIS) or invasive mucinous adenocarcinoma (IMA), depending on size, invasion, and multifocality. With *KRAS* mutations having been reported in mucinous cells both within the cyst and in the adjacent alveoli,^{7,9,10,13–16} and rare reports of associated metastases and mixed mucinous and non-mucinous adenocarcinoma,^{17,18} these lesions are now accepted by some pathologists as neoplastic (either as AIS or IMA).

Although the nature of these lesions is better established, there are few data on the outcome and follow-up of these rare lesions, even in literature reviews.¹⁹ In this study, we describe a series of 37 mucinous adenocarcinoma cases arising from CPAMs, looking at the histopathological features (including growth patterns, nuclear features, and

location of mucinous proliferation), genetic abnormalities, surgical procedures, and clinical follow-up data, with the aim of identifying key features and proposing recommendations that can be used for future management.

Materials and methods

CASE SELECTION

A review of the archives of the Royal Brompton Hospital (London, UK) and Erasmus University Medical Centre (Rotterdam, The Netherlands) for adenocarcinomas resected with associated cystic changes revealed 42 cases (Royal Brompton Hospital, $n = 34$; Erasmus University Medical Centre, $n = 8$) within a 34-year period, either as consultation cases ($n = 18$) or routine diagnostic cases ($n = 24$). Five cases were excluded as a result of insufficient evidence supporting the presence of a cystic lesion pre-dating tumour development, and were viewed as adenocarcinomas showing cystic change as part of their presentation.^{20,21} The slides for the remaining 37 cases were reviewed by three thoracic pathologists (W.-C.C., A.G.N., and J.H.T.), and the type of adenocarcinoma and CPAM, tumour location, location of mucinous proliferation (intracystic—defined as limited to bronchial-like or bronchiole-like cystic areas lined by mainly respiratory-type cells; or extracystic—defined as extending into alveolar-like parenchyma lined by pneumocytes), growth patterns, nuclear atypia, necrosis, lymphovascular invasion, tumour spread through airspace (STAS), pleural invasion and synchronous atypical adenomatous hyperplasia (AAH) were recorded. Cases with more than one specimen all had tissue from both samples available for review. Clinical data, tumour staging²² and follow-up were also recorded. Five of these cases (cases 12, 15, 22, 26, and 28) have been previously reported in case reports or case series.^{8,13,23,24}

MUTATIONAL ANALYSES

Detection of *KRAS*, *EGFR* and other mutations was performed on 11 cases as part of a routine clinical workup in five institutions (Royal Brompton Hospital,

Erasmus University Medical Centre, Oxford University Hospitals, Cancer Centre of Léon Bérard, and Centre Hospitalier Universitaire de Grenoble).

STATISTICAL ANALYSES

Comparisons between continuous variables were performed with one-way ANOVA, and Fisher's exact test and the chi-square test were used to assess associations between categorical variables. Statistical significance was considered to be present if the *P*-value was <0.05 (two-sided). All statistical analyses were performed with the SPSS statistical software package (v.25.0; SPSS, Chicago, IL, USA) and GRAPHPAD PRISM (v.8.3.0; GraphPad, La Jolla, CA, USA).

Results

CLINICAL FEATURES

The patient cohort comprised 22 males and 15 females, and the mean age was 20.3 years (range, 0 days to 68 years), with 22 patients aged <18 years. The main presenting symptoms/signs were recurrent infections ($n = 4$), tachypnoea/dyspnoea ($n = 4$), cough ($n = 3$), pneumothorax ($n = 2$), chest discomfort ($n = 3$), and respiratory failure ($n = 2$). Two infant patients were intubated immediately after birth with a suspected diagnosis of congenital diaphragmatic hernia, diagnosed by the use of prenatal ultrasonography. The location of the cyst/tumour was available for 32 cases, with the predominant site being the left lower lobe ($n = 10$), followed by the right lower lobe ($n = 8$), the left lung, not stated ($n = 5$), the left upper lobe ($n = 4$), the right middle lobe ($n = 3$), the right upper and middle lobe ($n = 1$), and the right lung, not stated ($n = 1$). Tumour size ranged from 0.3 mm to 120 mm. Most patients underwent anatomical resections [lobectomy ($n = 28$), bilobectomy ($n = 1$), and pneumonectomy ($n = 2$)], with four cases treated with non-anatomical cyst resection. One patient underwent segmentectomy followed by lobectomy when adenocarcinoma was identified in the segmentectomy. One patient underwent biopsy of a mass in the lung contralateral to the cyst.

At the time of diagnosis, tumour stages at first presentation were stage 0 (pTis; $n = 22$), stage I (pT1 and pT2a; $n = 9$), stage II (pT2b and pT3; $n = 3$), and stage III (pT4; $n = 2$). One patient (case 28) was diagnosed with stage IV (cM1a) IMA on surgical lung biopsy of mass lesions arising in a background of preceding cystic lung disease. The clinical features are summarised in Table 1.

HISTOPATHOLOGICAL FINDINGS

With regard to the background cysts (Table 2), 33 were type 1 CPAMs and four were type 2 CPAMs, with smaller cysts being lined by bronchial/bronchiolar epithelium separated by underdeveloped/simplified alveoli. In one case, mucinous adenocarcinoma was diagnosed on biopsy without sampling of the cyst, but there was unequivocal evidence of a cyst pre-dating development of the tumour.

With regard to the tumours, 34 cases were purely mucinous adenocarcinomas, and three cases were mixed mucinous and non-mucinous adenocarcinomas. The majority were purely lepidic with mild nuclear atypia and no mitosis (Figure 1A,B). Of those with invasive patterns ($n = 5$; Figure 1C,D), all were lepidic-predominant with minor acinar, papillary or micropapillary patterns, showing mild to moderate nuclear atypia and increased mitotic activity. Two cases showed aerogenous spread into the adjacent alveoli, resembling STAS. Synchronous AAH was observed in the adjacent lung parenchyma in three cases. Necrosis, lymphovascular invasion and pleural invasion were not observed in any case. Of the four cases in which recurrence/residual tumour was observed, one (case 22) had both tumour and residual cyst in the completion lobectomy. The other three cases showed recurrent/residual tumour only (cases 7, 17, and 18). Surgical margins were not specifically sampled in the original CPAM specimen, so whether lesional tissue was present in the surgical margin could not be evaluated.

Tumour location was subdivided into involvement of cystic areas (intracystic) and extension into surrounding alveolar parenchyma (extracystic). Five cases were purely intracystic, 15 cases showed predominantly extracystic growth with a minor intracystic component (Figure 1B), and 17 cases were purely extracystic (Figure 1C,D; Table 2). Mixed mucinous and non-mucinous cell types, STAS and synchronous AAH were more likely to be seen in cases with purely or predominantly extracystic growth, although the difference did not reach statistical significance (Table 3).

MOLECULAR FINDINGS

Molecular testing was performed in 11 cases. Nine of 10 cases tested for *KRAS* mutations were positive, and showed either *KRAS* exon 2 G12V mutations (c.35G>T; cases 7, 9, 16, and 30) or *KRAS* exon 2 G12D mutations (c.35G>A; cases 28, 10, 12, 13, 18, and 28). In case 18, an additional *GNAS* p.R201H mutation was detected alongside the *KRAS* exon 2

Table 1. Clinical features of mucinous adenocarcinomas arising in congenital pulmonary airway malformation (CPAM)

No.	Age	Sex	Symptoms/signs	Location	Treatment	Size (mm)	TNM stage	Follow-up
1	0 days	M	Respiratory failure	LUL	Lobectomy	1.9	pTisNx	AFoD (63 months)
2	1 day	M	NA	Left	Lobectomy	0.4	pTisNx	Postoperative death (1 day)
3	2 days	M	Suspicion of congenital diaphragmatic hernia on prenatal ultrasonography	LUL	Lobectomy	0.8	pTisNx	NA
4	2 days	M	Respiratory failure	Left	Pneumonectomy	0.6	pTisNx	Postoperative death (12 days)
5	4 days	M	Tachypnoea	RLL	Lobectomy	1.2	pTisNx	AFoD (99 months)
6	10 days	F	Suspicion of congenital diaphragmatic hernia on prenatal ultrasound	Left	Pneumonectomy	0.3	pTisNx	AFoD (61 months)
7	12 days	F	Cyst resected in neonate	RUL/RML	Bilobectomy of CPAM; wedge biopsy of M1a recurrence	20	pT1bNx	M1a recurrence at 392 months, DoD (437 months)
8	14 days	M	Cyst resected in neonate	LUL	Lobectomy	9	pT1aNx	NA
9	21 days	M	NA	LLL	Lobectomy	0.6	pTisNx	AFoD (13 months)
10	1 month	F	Tachypnoea, dyspnoea, cough	RML	Lobectomy	3	pTisNx	NA
11	49 days	M	Tachypnoea, dyspnoea, respiratory acidosis	LLL	Lobectomy	0.9	pTisNx	AFoD (30 months)
12	6 months	M	No symptoms	RLL	Lobectomy	1	pTisNx	AFoD (385 months)
13	2 years	M	NA	NA	Lobectomy	10	pT1aNx	AFoD (5 months)
14	2 years	F	NA	RLL	Lobectomy	1	pTisNx	AFoD (25 months)
15	3 years	F	Recurrent infections	LLL	Lobectomy	2	pTisNx	NA
16	4 years	F	NA	NA	Lobectomy	1	pTisNx	AFoD (12 months)
17	11 years	F	NA	NA	Segmentectomy, then completion lobectomy	13	pT1bNx	Residual tumour in lobectomy, no further follow-up
18	13 years	M	Severe chronic asthma	LUL	Non-anatomical cyst resection of CPAM; lobectomy for RLL recurrence	45	pT2bN0	Recurrence at 15 years (with further lobectomy), AFoD (8 months after recurrence)*
19	15 years	F	NA	RLL	Lobectomy	20	pT1bNx	NA
20	15 years	M	Recurrent pneumothoraces	LLL	Lobectomy	2	pTisNx	AFoD (2 months)
21	17 years	M	NA	NA	Non-anatomical cyst resection	2	pTisNx	NA

Table 1. (Continued)

No.	Age	Sex	Symptoms/signs	Location	Treatment	Size (mm)	TNM stage	Follow-up
22	18 years	M	History of cyst with infections	LLL	Non-anatomical cyst resection, then completion lobectomy	6	pT1aNx	Residual/recurrence at 7 years (with further resection), AFoD (272 months)
23	22 years	F	NA	NA	Lobectomy	17 (multiple intralobar)	pT3Nx	NA
24	27 years	F	Recurrent infections	Right	Lobectomy	17	pT1bNx	NA
25	28 years	F	NA	Left	Lobectomy	4	pTisNx	NA
26	30 years	F	NA	RLL	Lobectomy	20	pT1bNx	NA
27	34 years	M	NA	RML	Lobectomy	3	pTisNx	NA
28	35 years	M	History of cyst (11 years before diagnosis) with infections	RML	Surgical lung biopsy of M1a disease only	15	cT3NxM1a	DoD (68 months)
29	35 years	F	NA	LLL	Lobectomy	3	pTisNx	NA
30	41 years	F	Flu-like symptoms, chest tightness	LLL	Lobectomy	3	pTisN0	NA
31	42 years	M	Chest wall discomfort, cough	RLL	Lobectomy	98	pT4N0	AFoD (1 month)
32	51 years	M	Pneumothorax	Left	Lobectomy	5	pTisNx	NA
33	56 years	M	No symptoms	LLL	Lobectomy	120	pT4N0	AFoD (46 months)
34	57 years	M	Dyspnoea	LLL	Lobectomy	31	pT2aN0	AFoD (115 months)
35	61 years	M	Infections	LLL	Lobectomy	2	pTisNx	AFoD (10 months)
36	64 years	F	NA	RLL	Non-anatomical cyst resection	4	pTisNx	NA
37	68 years	M	Cough, right chest pain	RLL	Lobectomy	45	pT2bN0	D cu (130 months)

AFoD, alive free of disease; D cu, died of unknown cause; DoD, died of disease; F, female; LLL, left lower lobe; LUL, left upper lobe; M, male; NA, not available; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

*After four cycles of adjuvant chemotherapy with cisplatin–pemetrexed.

G12D mutation observed in the original CPAM (Table 2). Four cases were tested for *EGFR* mutations and two for *ALK* rearrangement; all were negative.

CLINICAL FOLLOW-UP

Clinical follow-up data were available for 21 cases. Residual disease on completion lobectomy was observed in two patients (cases 17 and 22), one at 7 years and one in whom lobectomy followed segmentectomy. Two patients suffered recurrence at 32 years and 15 years after the initial diagnosis (cases 7 and 18); one of these (case 7) died

45 months after M1a recurrence. One patient (case 22) was found to have residual/recurrent disease 7 years after initial non-anatomical resection. One patient (case 28) died 68 months after presenting with M1a disease. Two patients (cases 2 and 4) died postoperatively, and one patient (case 37) died 130 months after diagnosis, from an unknown cause.

Discussion

This study shows that adenocarcinomas arising in CPAMs are typically indolent mucinous AISs or IMAs

Table 2. Histopathological and molecular features of mucinous adenocarcinomas arising in congenital pulmonary airway malformation (CPAM)

No.	CPAM type	Cell type	Location*	Lepidic (%)	Acinar (%)	Papillary (%)	Micropapillary (%)	Atypia	Mitoses (/2 mm ²)	STAS	AAH	KRAS
1	1	Mucinous	Extracystic	100	0	0	0	Mild	3	No	No	NA
2	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
3	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
4	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
5	2	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
6	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
7	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	G12V
8	1	Mucinous	Extracystic	100	0	0	0	Mild	4	No	No	NA
9	2	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	G12V
10	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	G12D
11	1	Mucinous	Intracystic	100	0	0	0	Mild	0	No	No	NA
12	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Moderate	1	No	No	G12D
13	1	Mucinous	Extracystic	100	0	0	0	Moderate	1	No	No	G12D
14	1	Mucinous	Intracystic	100	0	0	0	Mild	0	No	No	NA
15	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	WT
16	1	Mucinous	Extracystic	100	0	0	0	Moderate	0	No	No	G12V
17	1	Mixed	Extracystic	90	5	5	0	Moderate	0	No	Yes	NA
18	2	Mucinous	Extracystic	50	0	30	20	Moderate	1	No	No	G12D [†]
19	1	Mixed	Intracystic/ extracystic	100	0	0	0	Moderate	0	No	No	NA
20	1	Mucinous	Intracystic	100	0	0	0	Mild	0	No	No	NA
21	1	Mucinous	Intra/ extracystic	100	0	0	0	Mild	0	No	No	NA
22	1	Mucinous	Intracystic/ extracystic [‡]	100	0	0	0	Mild	0	No	No	NA
23	1	Mucinous	Intracystic/ extracystic	95	5	0	0	Mild	0	No	No	NA
24	1	Mixed	Intracystic/ extracystic	100	0	0	0	Mild	0	No	Yes	NA
25	2	Mucinous	Extracystic	100	0	0	0	Moderate	0	No	No	NA
26	1	Mucinous	Extracystic	100	0	0	0	Mild	0	No	No	NA
27	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	NA
28	1 [§]	Mucinous	Extracystic	100	0	0	0	Mild	2	No	No	G12D

Table 2. (Continued)

No.	CPAM type	Cell type	Location*	Lepidic (%)	Acinar (%)	Papillary (%)	Micropapillary (%)	Atypia	Mitoses (/2 mm ²)	STAS	AAH	KRAS
29	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	Yes	NA
30	1	Mucinous	Intracystic	100	0	0	0	Mild	0	No	No	G12V
31	1	Mucinous	Intracystic/ extracystic	75	5	0	20	Moderate	3	Yes	No	NA
32	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	NA
33	1	Mucinous	Intracystic/ extracystic	95	5	0	0	Moderate	1	No	No	NA
34	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	NA
35	1	Mucinous	Intracystic	100	0	0	0	Mild	0	No	No	NA
36	1	Mucinous	Intracystic/ extracystic	100	0	0	0	Mild	0	No	No	NA
37	1	Mucinous	Extracystic	100	0	0	0	Moderate	0	Yes	No	NA

AAH, atypical adenomatous hyperplasia; G12D, exon 2 Gly12Asp; G12V, exon 2 Gly12Val; NA, not available; STAS, tumour spread through airspace; WT, wild type.

*Intracystic: tumour cells are intracystic (defined as cysts otherwise lined by respiratory-type epithelium). Extracystic: tumour cells are extracystic (defined as extending into adjacent alveolar parenchyma lined by pneumocytes). Intracystic/extracystic: tumour cells are present in both areas (the predominant area is in bold).

[†]Associated with an exon 8 p.R201H *GNAS* mutation in the recurrence.

[‡]Residual/recurrent tumour and residual CPAM in completion lobectomy.

[§]Based on cyst size on imaging.

that are cured by anatomical resection of the cyst and surrounding lung, usually by lobectomy. However, some tumours show more aggressive histological subtypes, and, more importantly, independent of histology, can recur decades after initial resection of the cyst at an advanced stage, especially when resection is at a level less than lobectomy.

With regard to histopathological features, CPAMs with pure intracystic proliferation of mucinous adenocarcinoma cells are associated with lepidic growth and the absence of an invasive component, and all showed an indolent behaviour, with an excellent prognosis; in contrast, CPAMs with mixed intracystic/extracystic or pure extracystic mucinous proliferations were occasionally associated with invasive architectural patterns, STAS, and tumour recurrence or intrapulmonary metastasis. This suggests that the presence of extracystic mucinous proliferations alone should be viewed as a more aggressive feature even in the absence of stromal, pleural or vascular invasion, and a thorough examination of the resected specimen by the use of extensive sampling may be

warranted to rule out invasive components elsewhere.

Anatomical lung resection has been recommended as the optimal treatment for CPAMs, given the risk of malignant transformation.²⁵ In our series, there were four cases (cases 7, 17, 18, and 22; 10.8%) that had either residual disease on lobectomy or recurred years after the initial surgery; all but one initially received non-anatomical cyst resection. The ability of these mucinous adenocarcinoma cells to spread directly into alveolar parenchyma adjacent to the cystic areas and not be completely removed by non-anatomical resections is further exemplified by a case described by Summers *et al.*,¹⁴ in which an 8-year-old female with well-differentiated multifocal mucinous adenocarcinoma arising in CPAM diagnosed in the left lower lobe wedge biopsy was subsequently found to have residual tumour in the completion lobectomy and contralateral metastasis in the right lower lobe. Indeed, within a non-anatomical resection, it may be impossible with the naked eye at surgery or on preoperative imaging to definitively identify the border

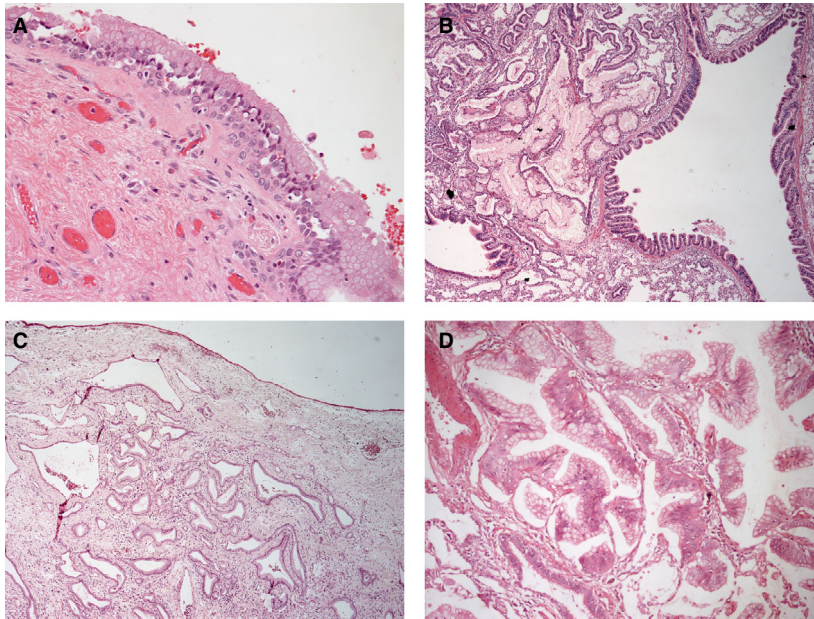


Figure 1. A, A few cases show purely focal intracystic proliferation of mucinous adenocarcinoma cells adjacent to respiratory epithelium, usually in a lepidic fashion (case 13). B, Mucinous adenocarcinoma cells growing in a lepidic pattern adjacent to a large cystic space lined by ciliated respiratory epithelium, consistent with type 1 congenital pulmonary airway malformation (case 6). C, Extracystic acinar growth set in a fibrotic stroma can be observed in some cases (case 27). D, Extracystic papillary or micropapillary growth may be present alongside lepidic growth in some cases (case 11).

between lesional and normal alveolar tissue outside of visible cysts. However, because cases with non-anatomical resection in our study were mostly historical cases without adequate sampling of the surgical margins, we were unable to confirm whether the resection margins contained residual CPAM lesional tissue. Given most CPAMs are lobar, with rare exceptions,^{26,27} anatomical resection would therefore seem more likely to achieve complete resection of the CPAM and any tumour therein. This is supported by a recent study of 44 infantile CPAMs with mucinous cell clusters in which resection by lobectomy was not associated with poor outcomes.²⁷ Although the numbers are small, these cases illustrate the importance of anatomical lung resection when a mucinous adenocarcinoma arising in a CPAM is identified, especially when disease extends beyond the cyst wall. Notably, we found that AAH was also present in 8.3% of cases, and there have also been previous reports of non-mucinous adenocarcinomas with or without AAH arising in CPAMs.^{28,29} These preneoplastic changes suggest that lung parenchyma in the vicinity of the cysts may have an increased propensity to undergo neoplastic change, and a field cancerisation effect might be responsible for their evolutionary origin.

There is an ongoing debate concerning the appropriate terminology for describing these mucinous cell proliferations, with many reports using the World Health Organization (WHO) terminology of 'mucinous adenocarcinoma' (including our study),^{9,10,14,16,30} and two recent studies using the terms 'AGCH' and 'mucinous cell clusters (MCCs)' to describe the mucinous cells.^{7,27} Although some have argued that these proliferations should not be classified with the use of a malignant or premalignant term, this view seems to be primarily based on a lack of malignant behaviour if complete resection is performed.²⁷ However, these proliferations are morphologically indistinguishable from those in adults, and this study shows evidence of recurrence and metastasis if complete resection is not performed, albeit with a very slow growth rate. In addition, genetic analysis has demonstrated that these mucinous cells frequently harbour mutations of *KRAS*, most commonly exon 2 G12D (c.35G>A), G12V (c.35G>T) and G12C (c.34G>T) mutations,^{7,9,10,13–16,30–32} which are similar to the *KRAS* mutations commonly found in mucinous adenocarcinomas arising *de novo*, typically in smokers.^{33–37} In addition to *KRAS* mutations, Lantuejoul *et al.* demonstrated loss of heterozygosity at the tumour suppressor genes *FHIT*, *Rb*, and *p16^{INK4}*, not only in the

Table 3. Subgroup comparison of histopathological features based on the location of mucinous proliferation

Features	Intracystic (N = 5)	Intracystic/ extracystic (N = 15)	Extracystic (N = 17)	P-value
CPAM type (n)				
1	5	15	13	0.071
2	0	0	4	
Cell type (n)				
Mucinous	5	13	16	0.576
Mixed	0	2	1	
Invasive component (n)				
Absent	5	12	12	0.366
Present	0	3	5	
Nuclear atypia (n)				
Mild	5	11	11	0.295
Moderate	0	4	6	
Severe	0	0	0	
Mitoses per 2 mm² (n)				
Range	0	0–3	0–4	0.395
Mean (SD)	0 (0)	0.33 (0.82)	0.65 (1.22)	
STAS (n)				
Absent	5	14	16	0.844
Present	0	1	1	
Synchronous AAH (n)				
Absent	5	13	16	0.576
Present	0	2	1	

AAH, atypical adenomatous hyperplasia; CPAM, congenital pulmonary airway malformation; SD, standard deviation; STAS, tumour spread through airspace.

extracystic component, but also in the intracystic component.¹³ Consistent with the previous studies, exon 2 G12D and G12V mutations were also detected in nine of 10 cases in our cohort, two of which eventually recurred 15 and 32 years later. Furthermore, STAS can also be observed in mucinous

adenocarcinomas arising in CPAMs similar to those arising *de novo*,³⁸ although the frequency is low (2/37; 5.4%). We therefore believe that it is more appropriate to use the WHO criteria for adenocarcinoma and AIS for these lesions, although we recognise that this is an area that requires more data in the hope of achieving a consensus.³⁹

The limitations of the current study are that the data are incomplete, being retrospective, spanning >30 years, and often being from referred cases with limited follow-up information. Nevertheless, outcomes for which data are available do provide information that helps to suggest the management of future cases in terms of type of resection and duration of follow-up. We also have a relative lack of genetic studies, but data on those tested show recurring *KRAS* mutations, similar to those in adults with IMAs.

In summary, most cases of adenocarcinomas complicating CPAMs are purely lepidic IMAs or mucinous AISs, predominantly arising in type 1 CPAMs, although there are rare type 2 or 3 cases. CPAMs limited to intracystic bronchiolar-type proliferation are associated with the absence of an invasive component and an excellent prognosis, whereas those with extracystic proliferation into alveolar tissues may be associated with more aggressive behaviour and advanced stage, even in the absence of stromal, pleural or lymphovascular invasion. Tumours share the same spectrum of *KRAS* mutations as those in adults with *de-novo* IMA, and further studies investigating the genetic stability of the background lung are warranted. Most cases are cured with lobectomy, but non-anatomical resection is associated with recurrence/residual disease. Long-term follow-up, the nature of which would probably be empirical and depend on factors including patient age, stage, and completeness of resection (R status), may be needed, as recurrence can occur decades later.

Conflicts of interest

A. G. Nicholson has received: consultancy fees from Merck, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, BMS, Roche, and Abbvie; lecture fees from AstraZeneca; and research grant from Pfizer. S. Popat has received consultancy fees from BMS, Roche, Takeda, AstraZeneca, Pfizer, MSD, EMD Serono, Guardant Health, Abbvie, Boehringer Ingelheim, OncLive, Medscape, Incyte, Paradox Pharmaceuticals, Blueprint, and Lilly. S. Lantuejoul has received consultancy fees from MSD, AstraZeneca, BMS, and Lilly. Wei-Chin Chang has received consultancy fees from

Boehringer Ingelheim. The remaining authors declare no conflicts of interest.

Author contributions

Wei-Chin Chang co-designed the research study, analysed the data, performed the research, and wrote the paper. A. G. Nicholson co-designed the research study and critically reviewed the paper. Yu Zhi Zhang assisted in collecting the clinical follow-up data. J. L. Wolf, S. M. Hermelijn, J. M. Schnater, J. H. von der Thüsen, S. Lantuejoul, B. Mastroianni, C. Farver, F. Black and S. Popat contributed the consultation cases, clinical follow-up data, and molecular data.

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