MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Congenital Pulmonary Airway Malformation in Adults and Mucinous Adenocarcinoma

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE ANATOMIA PATOLÓGICA

Trabalho realizado sob a orientação de:

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MARÇO/2021

CONGENITAL PULMONARY AIRWAY MALFORMATION IN ADULTS AND MUCINOUS ADENOCARCINOMA

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Março 2021

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RESUMO

A malformação congénita das vias aéreas pulmonares (MCVAP), é a malformação congénita pulmonar mais comum, diagnosticada no período pré-natal ou em recém-nascidos sintomáticos, é rara na idade adulta. Uma série de MCVAP em adultos foi diagnosticada no Centro Hospitalar e Universitário de Coimbra - Portugal, durante doze anos (desde 2008 a 2019). Foi desenvolvida uma análise descritiva de 27 casos que foram revistos relativamente a achados clínicos, radiológicos e histopatológicos, reportando-se também a incidência do adenocarcinoma mucinoso.

Os doentes apresentaram idade mediana de 48.0 anos no momento do diagnóstico e predominância do género feminino (1:2.3). A maioria das lesões estava localizada nos lobos inferiores e os doentes (24/27) apresentaram sintomas que necessitaram de investigação clínica e radiológica. De acordo com a classificação de Stocker, a maior parte dos casos foram classificados como tipo 1 (19/27), e os restantes como sendo do tipo 2 (8/27). Esta malformação predispõe os doentes a infeções pulmonares recorrentes, observadas em praticamente metade dos doentes. A aspergilose associada a esta lesão pulmonar foi igualmente reportada.

Em cinco casos, foram diagnosticados adenocarcinomas mucinosos, tratando-se de dois casos do tipo 1 e três casos do tipo 2. A idade mediana destes doentes era superior à dos doentes sem neoplasia (74.0 vs. 42.0). Tratando-se de casos raros, poderá ser um indício de que a MCVAP, nomeadamente dos tipos 1 e 2, poderá ser considerada uma potencial condição pré-neoplásica.

A gestão de doentes adultos assintomáticos com MCVAP permanece controversa e a incidência de carcinomas do pulmão poderá estar a ser subestimada por diagnóstico incompleto em peças cirúrgicas de resseção tumoral. A série apresentada indica que a resseção das lesões pode ser o método mais eficaz para a prevenção da transformação maligna, bem como para o diagnóstico de MCVAP em adultos.

Palavras-chave: malformação congénita das vias aéreas pulmonares; pulmão; adenocarcinoma; adulto.

ABSTRACT

Congenital pulmonary airway malformation (CPAM) is the most common developmental congenital malformation of the lung, diagnosed antenatally or symptomatic in infants, is rare in adulthood. A series of CPAM in adult patients was diagnosed at *Centro Hospitalar e Universitário de Coimbra – Portugal* during 12 years (2008 to 2019). A descriptive analysis of 27 CPAM cases was developed and reviewed concerning clinical, radiological, and histopathological findings, with reported incidence of mucinous adenocarcinoma.

Patients median age was 48.0 years at diagnosis, with female predominance (1:2.3). Most lesions were located at the lower lobes and patients (24/27) presented with symptoms that led to a clinical and radiological investigation. According to Stocker's classification, most cases were classified as CPAM type 1 (19/27) and the remaining as CPAM type 2 (8/27). This malformation predisposes to recurrent pulmonary infections, seen in almost half of the patients. Aspergillosis CPAM associated was also reported.

In five cases, concerning two cases of CPAM type 1 and three cases of type 2, mucinous adenocarcinoma was diagnosed. The median age at diagnosis of these five patients was superior to patients without lung tumors (74.0 vs. 42.0). These rare cases might indicate CPAM types 1 and 2, as potential pre-neoplastic conditions.

The management of asymptomatic CPAM in adult patients remains controversial and pulmonary carcinomas incidence might be underestimated due to CPAM incomplete diagnosis in tumoral surgical specimens. The presented series supports surgical resection as the most effective way to prevent malignant transformation, as well as CPAM diagnosis in adults.

Keywords: cystic adenomatoid malformation of lung, congenital; lung; adenocarcinoma; adult.

1. INTRODUCTION

Congenital pulmonary airway malformation (CPAM), originally known as congenital cystic adenomatoid malformation (CCAM) (1), is the most common developmental malformation of the lung with a prevalence of 1 in 25 000 to 35 000 pregnancies. (2) This condition correlates with up and down bronchioles maturation disturbance, with unknown exact pathogenesis and is currently classified into five types (type 0 to 4) accordingly to Stocker classification, based on the size of the “cystic” spaces, the topographic micro-anatomical location of the lesions and histopathological characteristics of the “cystic” walls. (1)

CPAM is diagnosed either antenatally by ultrasonography, in symptomatic neonates or infants with respiratory distress syndrome in 80% of cases. (3) Occasionally, children go through their entire childhood without exhibiting symptoms (4), till adulthood when incidentally or during workup due to recurrent pneumonia, pneumothorax, hemoptysis or chronic obstructive pulmonary disease (COPD) (2), radiologic imaging using X-Ray and CT scan are complemented with histopathological examination for establishing the final diagnosis. (5)

CPAM has been recognized as precursor lesion of mucinous adenocarcinoma (MA), usually associated with type 1 CPAM following genetic alterations of mucous CPAM cells. (6–8) However, CPAM evolution to MA is considered a rare event with unascertained causes.

The prevalence of CPAM in adults is unknown due to its rarity and possible asymptomatic course. In Portugal, there are no reports characterizing an adulthood population with CPAM, to the best of our knowledge. We hereby present a series of adult CPAM concerning twelve years of archival study and compare population clinicopathological features with published literature. Cases of CPAM-related pulmonary carcinomas are also reported.

2. MATERIALS AND METHODS

In the aim of this descriptive retrospective study an anonymized list of CPAM cases was retrieved from Pathology archives of *Centro Hospitalar e Universitário de Coimbra (CHUC) - Portugal* concerning 12 years (2008 to 2019), including gender, age at diagnosis time, smoking-status, respiratory diseases (asthma, COPD), other related symptoms, pulmonary anatomical location, surgical procedure, CT scan description and additional pathological examination findings.

Adult population (≥ 18 years) at diagnosis, totalized 27 patients. Two pathologists reviewed all cases using hematoxylin and eosin (HE) stain and PAS-D, following Stocker classification. Adenocarcinomas were classified according to 2015/2020 WHO classification. The following immunohistochemical panel was applied: CK7, CK20, CDX2 and TTF-1.

All statistical analysis were performed with SPSS statistical software package (v.25.0; SPSS, Chicago, IL, USA). Descriptive statistics included the median for continuous variables and absolute and relative frequency for categorical variables. Chi-square, Fisher's Exact and Mann-Whitney tests were used to establish associations and differences between variables. A p-value inferior to 0.05 was considered statistically significant.

This retrospective study followed the rules defined by the Ethical Committee of the Faculty of Medicine of the University of Coimbra concerning archival cases.

3. RESULTS

A total of 27 surgical biopsies/lobectomies of adult patients allowed CPAM diagnosis during twelve years at *CHUC*: eight men and 19 women, with a male:female ratio of 1:2.3. Age ranged between 20 and 85 years, with a median age at diagnosis of 48.0 years. Six patients presented asthma and two COPD; 21 patients were non-smokers and 10 patients had a registry of previous lung infections in their medical records, two of them presenting three or more episodes of pneumonia, including during childhood.

Twenty-four patients presented with symptoms that led to clinical and radiological investigation: 20 patients presented with cough, fever or pain, three with hemoptysis and one with dyspnea. The remaining three patients had CPAM recognized on routine chest scans.

Imaging reports described the lesions as nodules or cavitated masses in more than half of the cases (17 patients). Other less common radiological descriptions included bronchiectasis, air bubbles, abscess, pulmonary sequestration or pneumatocele.

The majority of patients underwent lobectomy (18 patients) and the remaining were submitted to surgical biopsies. The pulmonary incidence of CPAM is described in **Table 1.**

Table 1. CPAM – pulmonary incidence

n (Variable, %)	CPAM	Surgical biopsy
Location		
Right lower lobe	12 (44.4)	4 (14.8)
Left lower lobe	7 (25.9)	3 (11.1)
Left upper lobe	3 (11.1)	1 (3.7)
Right middle lobe	3 (11.1)	1 (3.7)
Right upper lobe	2 (7.4)	0 (0.0)

On histopathological analysis, all CPAM cases presented with multicystic lesions lined by respiratory-type epithelium. Stocker type 1 was the most common CPAM type, diagnosed in 19 patients. Thin-walled large cysts were lined by pseudostratified ciliated columnar epithelium interspersed with mucinous PAS-D-positive cells and with underlying fibro-elastic tissue. CPAM type 2 accounted for the remaining eight cases, consisting of multiple smaller cysts, resembling respiratory dilated bronchioles lined by columnar or cuboidal epithelium; these cysts were surrounded by simplified alveolar parenchyma. (**Figure 1**).

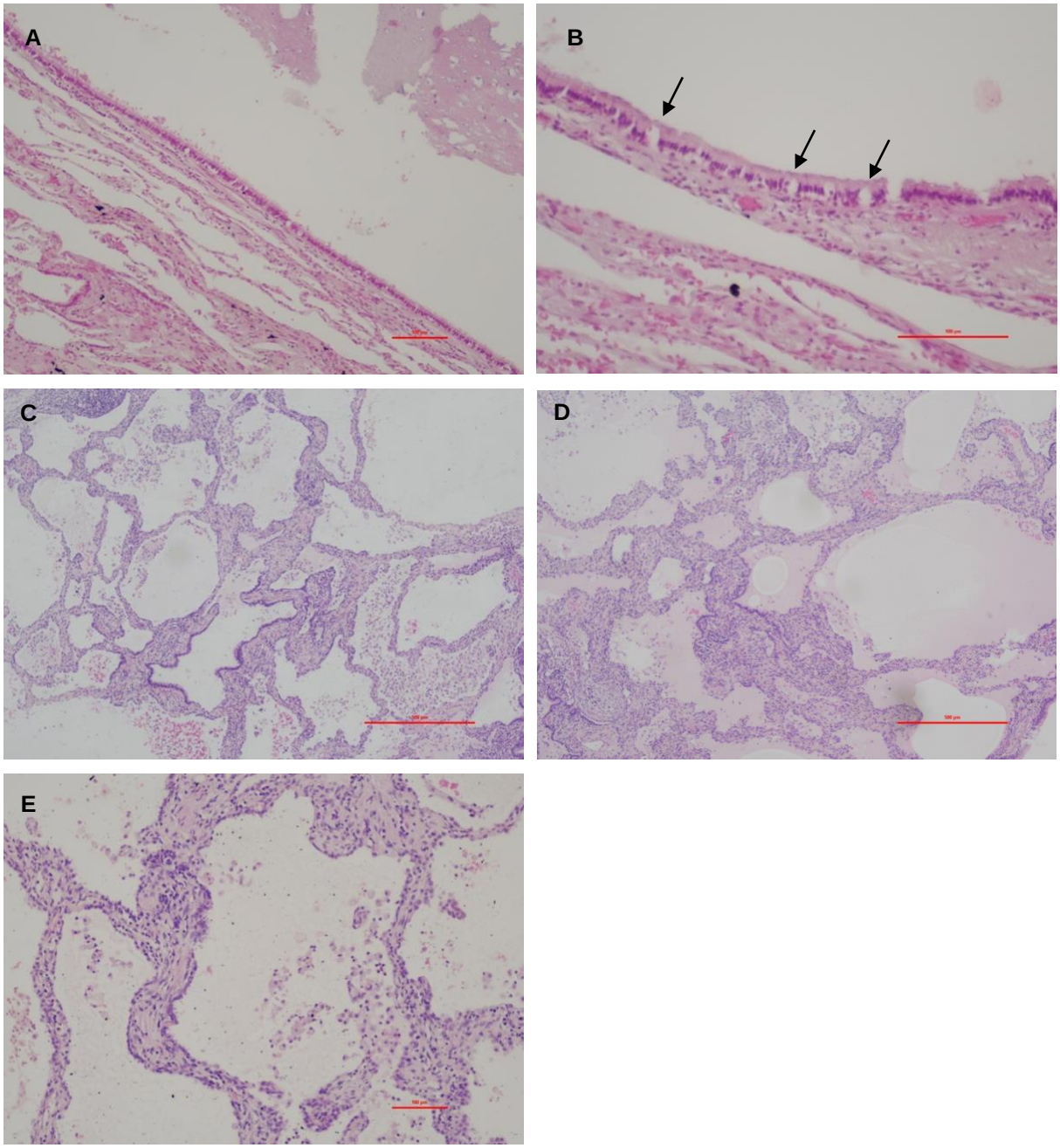

Figure 1. Type 1 CPAM (A) Cyst lined by columnar and ciliated pseudostratified columnar epithelium, which overlies a wall of connective tissue (HE, x10) (B) and mucinous/goblet cells in the epithelium (arrows) (HE, x200). Type 2 CPAM (C, D) Multiple cysts lined by cuboidal epithelium, presenting numerous bronchiole-like structures; there was no communication between the cystic structures, separated by mesenchymal walls with small lymphocytes; (HE, x40) (E) cysts, with walls composed by connective tissue, fusiform cells and scattered lymphocytes; cuboidal epithelium with nuclear atypia (HE, x100/200)

Eight CPAM cases showed associated organizing pneumonia, defined by an alveolar exsudate of fibrin and neutrophils, inflammatory myofibroblastic polyps and hyaline areas. Two cases had associated pulmonary aspergillosis.

CPAM developed adenocarcinoma corresponded to 5/27 cases. Clinical features are reported in **Table 2.** Strong tumor suspicion had been raised on imaging studies, and four out of the five patients were symptomatic. The median (Mdn) age at diagnosis of these patients was 74.0, significantly superior to the median age of the diagnosis of patients with CPAM without lung tumors at diagnosis (Mdn= 42.0), (U= 92.500, z= 2.345, p= .016).

Table 2. Mucinous adenocarcinoma in CPAM – patients clinical features

n (Variable, %)	Concomitant MA
Presentation	
Cough and/or fever and/or pain	3 (60.0)
Hemoptysis	0 (0.0)
Dyspnea	1 (20.0)
Asymptomatic/Occasional	1 (20.0)
Sample origin	
Lobectomy	4 (80.0)
Surgical biopsy	1 (20.0)
Location	
Right lower lobe	3 (60.0)
Left lower lobe	1 (20.0)
Left upper lobe	1 (20.0)
CT report	
Mass/nodule	5 (100.0)
Associated findings	0 (0.0)
CPAM classification	
CPAM Type 1	2 (40.0)
CPAM Type 2	3 (60.0)
Previous pneumonia	1 (20.0)

Mucinous adenocarcinomas had acinar pattern predominance, with cells presenting basally oriented nuclei with minimal atypia and columnar morphology with abundant intracytoplasmatic mucin. **(Figure 2)** The cells expressed cytoplasmatic CK7 and CK20, without TTF-1 or CDX2

expression. Regarding concomitant CPAM characterization, two cases were type 1 CPAM and three cases were type 2 CPAM.

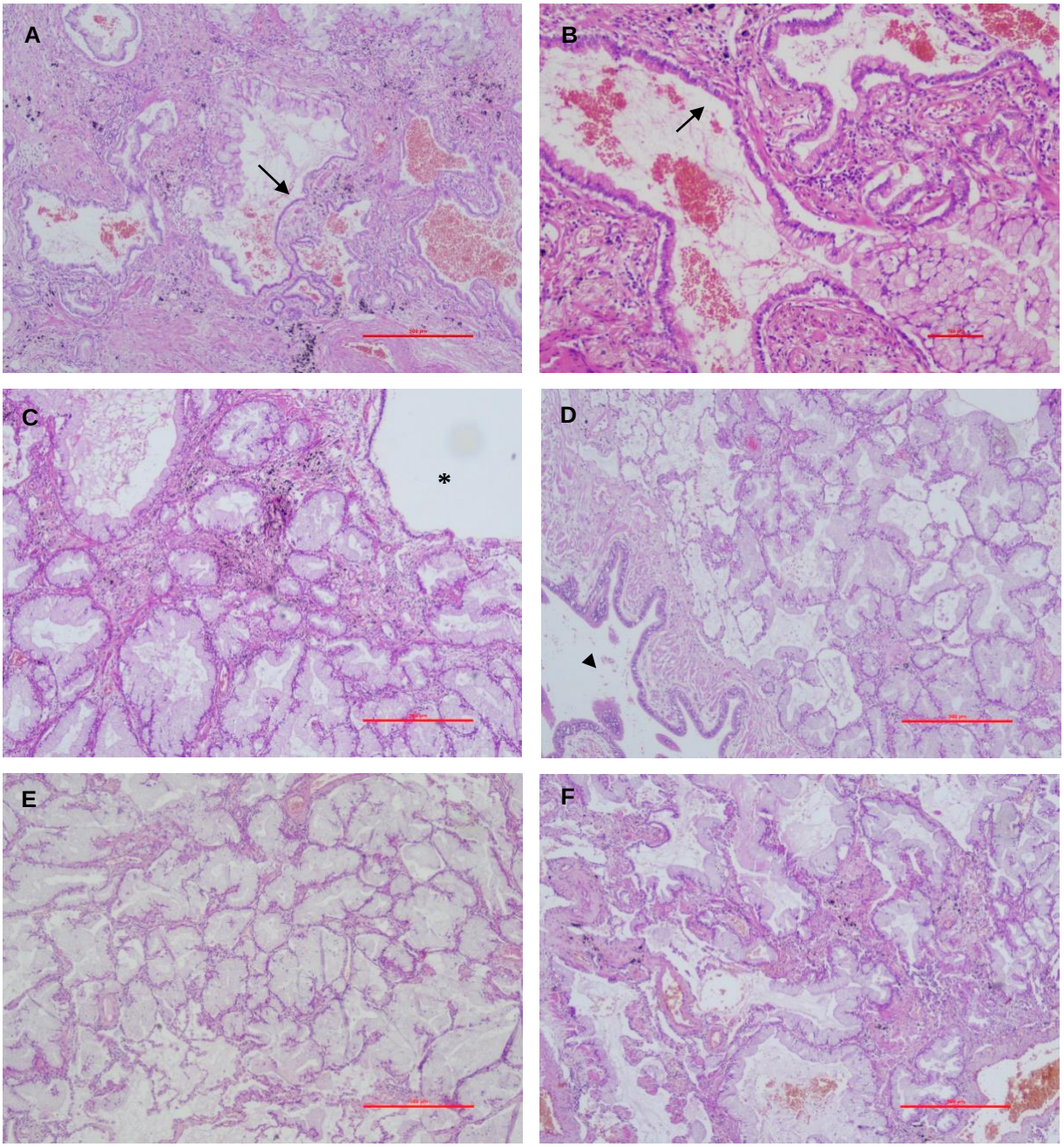

Figure 2. Mucinous adenocarcinoma developed in CPAM type 2. (A, B) Multiple cysts lined by cuboidal epithelium (arrows) and in part by neoplastic epithelium (C, D, E, F) Mucinous adenocarcinoma constituted by mucinous cells in acinar pattern nearby a cyst (*) and a bronchiole-like cyst (arrowhead).

4. DISCUSSION

CPAM Characterization

Defective morphogenesis of the lung preceding CPAM occurs at either different development stages and different tracheobronchial tree levels, explaining the morphology in CPAM types. Still not completely characterized, the disproportion between cell proliferation and apoptosis during organogenesis has been suggested as the pathological mechanism. (9,10) Molecular alterations such as abnormalities in chromosome 18, TTF-1 mutational disruption and high expression levels of HoxB5 are pointed as possible causes for CPAM establishment. (2,11)

In 1977, Stocker *et al.* (12) proposed a CPAM classification into three types and in 2002, added two more subtypes. (1) The current classification dividing CPAM into five groups intends to reflect the stage/level where the tracheobronchial tree development was arrested. CPAM types rely on clinical, radiological and pathologic features, including macroscopic examination and microscopic analysis.

Type 0, accounting for 1 to 3% of CPAM cases, represents an abnormality of the trachea and mainstem bronchi. Usually, the lesion involves all lobes of the lungs and is incompatible with life at birth.

Type 1 is the most prevalent CPAM type, representing 60 to 70% of the cases. It is composed of bronchial/bronchiolar-like structures. Thin-walled cysts occupy one lobe in about 95% of patients (1 to 10 cm). Microscopically, the largest cysts are lined by pseudostratified columnar epithelium overlying a wall of fibro-muscular connective tissue and occasional cartilage islands. Mucogenic epithelium may be present in 35 to 50% of cases and may represent a pre-malignant component. This lesion may go undetected for years until presenting with symptoms in adulthood. This type is resectable and has good prognosis.

Type 2 has bronchiolar origin and is the second most frequent CPAM type, accounting for 15 to 20% of cases. The lesion is small, composed of multiple small cysts (0.5 to 1.5 cm) lined by a smooth hyaline membrane, limited to one lobe, and blends with adjacent normal parenchyma. Microscopically, the spaces are lined by cuboidal to low columnar epithelial cells. This type may be associated with other congenital anomalies in 60% of cases (13) and, therefore, carries a poor prognosis. Renal agenesis and dysgenesis, cardiovascular anomalies (as Tetralogy of Fallot), persistent truncus arteriosus, diaphragmatic hernia, small intestine anomalies (jejunal atresia), extralobar sequestration, syringomyelia and skeletal anomalies

have been described. (1,9,14) However, in the absence of concomitant anomalies, CPAM type 2 is usually resectable and has a good prognosis.

Type 3 involves an entire lobe or an entire lung and accounts for 5 to 10% of CPAM cases. It has small thin-walled cysts (0.5 to 1.5 cm) lined by low cuboidal epithelium and can produce mediastinal shift and compression of the adjacent lung. The prognosis is usually poor.

Type 4 accounts for about 10% of cases of CPAM and is commonly localized to one lobe, where large thin-walled cysts (up to 10 cm) are lined with type 1 and type 2 alveolar cells. Surgical resection of the lesion is associated with a good prognosis.

According to published series and case reports, type 1 and type 2 CPAMs are the most common types found in the adult population and with better prognosis. (2,3,5,9,11,15–19) The presented series is concurrent with reported type 1 and type 2 CPAMs predominance.

Pogoriler *et al.* recently proposed a new natural distribution of CPAM subtypes, rejecting CPAM type 1 as the most common overall in change with type 2, justified by the small proportion of prenatally diagnosed CPAM type 1. (20) This result contrasts with most adult and infant series, including our results, where type 1 CPAM has been the most prevalent. Type 1 CPAM highest prevalence might reflect a bias toward symptomatic individuals and, therefore, more frequently detected and resected than type 2 cases, that can undergo undetected when not associated with other malformations. In fact, none of the type 2 CPAM cases in our series had registries of other malformations. However, most type 2 CPAM reported in the literature concern antenatally or symptomatic neonates or children. Moreover, since this lesion usually consists of multiple small cysts lying with normal adjacent lung parenchyma, it is less likely to cause symptoms and perhaps more challenging to identify on image studies. The absence of other congenital malformations enables CPAM to go undetected theoretically indefinitely. We theorize that keeping asymptomatic in the adult population prevents its recognition, and then type 2 CPAM becomes rarely reported.

Recurrent pulmonary infections are the most common complication of previously asymptomatic or oligosymptomatic CPAM patients. (5) Accordingly, in our series almost half of the patients presented organizing pneumonia on histological examination and many patients presented with symptoms at diagnosis (24/27), while the rest were incidental findings (3/27). This high prevalence of lung infections is consistent with values reported in large series of CPAM, which range from 35% to 50%. (3,11,21) Moreover, these common recurrent infections

also explain the rarity of CPAM diagnosis in adults, due to parenchymal morphology alterations. (22)

Two aspergillosis cases associated with type 1 CPAM were detected in the presented series: one patient presented with hemoptysis, and the second with cough and fever. Aspergillosis within CPAM is very rare, described in a few reports. (17,23,24) It can originate in residual cavitary lesions and can be present for years without symptoms. However, hemoptysis becomes the most common symptom and can be fatal.

Female predominance contrasted with most series where gender predilection has been irrelevant. (25) In adults a systematic review of 60 adult CPAM cases showed no gender preference (male: female ratio of 1:1) (3), while a smaller series (11 cases) reported male predominance with male:female ratio of 1.75:1 (16), but others present female predominance with a male:female ratio of 1:1.25 (9 cases). (5)

CPAM generally affects left and right sides equally and most CPAM patients have lower lobe lesions. (26) Larger series present a percentage of 65% of cases located in the lower lobes. (3) We found concordant results regarding the location, as most cases were also present in lower lobes (19/27) and reported with right-side predilection (17/27).

CPAM Associated Mucinous Adenocarcinoma

Mucinous CPAM cells may undergo genomic imbalances, increased proliferation rates, decreased apoptosis and dysregulated paracrine growth of cells and matrix, integrating KRAS mutations. Molecular changes are accompanied by a spectrum of mucinous cells proliferation, either intracystic or extracystic, before adenocarcinoma growth.

Loss of heterozygosity (LOH) at $p16^{IN\ pK4}$ locus with microsatellite alterations has been demonstrated in both CPAM and MA. Also, LOH at *FHIT* gene and *Rb* loci were seen. These findings justify the consideration of mucinous cells as MA precursors. (7) Malignant mucinous cells are described to form layers and outgrow the CPAM lesion boundary, creating an invasive tumor. (27)

The estimated incidence of MA in type 1 CPAM in the literature is around 1%. (28) A slightly higher prevalence is reported by Hamanaka *et al.*, reviewing 60 cases where two cases presented with MA (one case with CPAM type 1 and the other CPAM type was not classified). (3) In all 27 cases reviewed in our series, five patients presented with concomitant MA, a much

higher incidence percentage. As the majority of CPAM cases are diagnosed during childhood, the real incidence of neoplasms in CPAM may be underrecognized.

Surgical treatment in childhood is performed to prevent complications of CPAM. (4) Adults are mainly asymptomatic during most of their lives. In our series four out of five patients with MA were symptomatic, which led to the diagnosis of both MA and CPAM lesions.

Consistent with the literature, MA was present in older patients (74.0 vs. 42.0 years), suggesting that the incidence of MA but also the prevalence of CPAM in adults are underestimated. When adult CPAM incidence is searched, pulmonary carcinoma still keeps underreported.

Three out of five reported MA cases appeared in type 2 CPAM context. Malignant transformation is predominantly associated with type 1 CPAM and rarely described in association with type 2 CPAM, with only a few reports concerning the pediatric population. Koh *et al.* presented a case of MA in a neonate with type 2 CPAM (29) and recently four malignant transformation cases were described in type 2 CPAM, one in an adult patient. (15) Some authors reported MA cases in a setting of both CPAM 1 and 2 in the same case. (30,31)

5. CONCLUSION

CPAM in adults has not been commonly recognized, but its prevalence among asymptomatic adult patients may be higher than previously reported. Mucinous adenocarcinoma high prevalence in this series may suggest that resecting CPAM lesions may be the best strategy to prevent malignant transformation that can occur at any age. Additional research in this topic, especially regarding the progression of CPAM type 2 to MA, will clarify etiopathogenesis in the future.

6. REFERENCES

1. Stocker JT. Congenital pulmonary airway malformation—a new name for and an expanded classification of congenital cystic adenomatoid malformation of the lung. Histopathology. 2002;41(2):424–58.
2. Baral D, Adhikari B, Zaccarini D, Dongol RM, Sah B. Congenital Pulmonary Airway Malformation in an Adult Male: A Case Report with Literature Review. Case Reports in Pulmonology. 2015;2015:1–6.
3. Hamanaka R, Yagasaki H, Kohno M, Masuda R, Iwazaki M. Congenital cystic adenomatoid malformation in adults: Report of a case presenting with a recurrent pneumothorax and a literature review of 60 cases. Respiratory Medicine Case Reports. 2019 Jan 1;26:328–32.
4. Leblanc C, Baron M, Desselas E, Phan MH, Rybak A, Thouvenin G, et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. Vol. 176, European Journal of Pediatrics. Springer Verlag; 2017. p. 1559–71.
5. Gorospe L, Muñoz-Molina GM, Ayala-Carbonero AM, Fernández-Méndez MÁ, Arribas-Marcos Á, Castro-Acosta P, et al. Cystic adenomatoid malformation of the lung in adult patients: Clinicoradiological features and management. Clinical Imaging. 2016 May 1;40(3):517–22.
6. Benouaich V, Marcheix B, Begueret H, Brouchet L, Velly JF, Jougon J. Malignancy of congenital cystic adenomatoid malformation of lung in aged. Asian Cardiovascular and Thoracic Annals. 2009 Dec;17(6):634–6.
7. Lantuejoul S, Nicholson AG, Sartori G, Piolat C, Danel C, Brabencova E, et al. Mucinous Cells in Type 1 Pulmonary Congenital Cystic Adenomatoid Malformation as Mucinous Bronchioloalveolar Carcinoma Precursors [Internet]. 2007. Available from: http://journals.lww.com/ajsp
8. Mani H, Shilo K, Galvin JR, Stocker JT, Franks TJ. Spectrum of precursor and invasive neoplastic lesions in type 1 congenital pulmonary airway malformation: Case report and review of the literature [7]. Vol. 51, Histopathology. 2007. p. 561–5.
9. Malinova D v., Kolova PL, Radev RS. Congenital Cystic Adenomatoid Malformation Of The Lung: A Case Report And Review Of The Literature. Journal of Biomedical and Clinical Research [Internet]. 2015 Dec 1;8(2):160–3. Available from: http://content.sciendo.com/view/journals/jbcr/8/2/article-p160.xml
10. Hsu JS, Zhang R, Yeung F, Tang CSM, Wong JKL, So M-T, et al. Cancer gene mutations in congenital pulmonary airway malformation patients. ERJ Open Research. 2019 Feb;5(1):00196–2018.

11. McDonough RJ, Niven AS, Havenstrite KA. Congenital pulmonary airway malformation: A case report and review of the literature. Vol. 57, Respiratory Care. 2012. p. 302–6.
12. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung: classification and morphologic spectrum. Human Pathol. 1977;(8):155–71.
13. Disu E, Kehinde O, Anga A, Ubuane P, Itiola A, Akinola I, et al. Congenital pulmonary airway malformation: A case report of a rare cause of neonatal respiratory distress and review of the literature. Nigerian Journal of Clinical Practice. 2019;22(11).
14. Bush A, Chitty L, Harcourt J, Hewitt RJ, Nicholson AG. Congenital Lung Disease. In: Kendig's Disorders of the Respiratory Tract in Children. Elsevier; 2019.
15. Chang WC, Zhang YZ, Wolf JL, Hermelijn SM, Schnater JM, von der Thüsen JH, et al. Mucinous adenocarcinoma arising in congenital pulmonary airway malformation: clinicopathological analysis of 37 cases. Histopathology. 2020 Feb 1;
16. Barreiro TJ, Henn L, Ingnam S, Sypert M. Congenital pulmonary airway malformation in a 36 year-old female. Respiratory Medicine Case Reports. 2016;17:34–6.
17. Feng A, Cai H, Sun Q, Zhang Y, Chen L, Meng F. Congenital cystic adenomatoid malformation of lung in adults: 2 rare cases report and review of the literature [Internet]. 2012. Available from: http://www.diagnosticpathology.org/content/7/1/37
18. Duarte JC, Ferreira PG, Alfaro TM, Carvalho L, Ferreira AJ. Cystic adenomatoid pulmonary malformation in adults: A retrospective study in a tertiary university hospital. Vol. 23, Revista Portuguesa de Pneumologia (English Edition). Elsevier Doyma; 2017. p. 109–10.
19. Yoo J, Mi Lee Ji Han Jung S, Im Ahn M, Gon Cho D, Jin Kang Kyo Young Lee S, Jin Kang S. Adenocarcinoma Arising in Type 1 Congenital Cystic Adenomatoid Malformation: A Case Report and Review of the Literature 396 396 Corresponding Author. Vol. 42, The Korean Journal of Pathology. 2008.
20. Pogoriler J, Swarr D, Kreiger P, Adzick NS, Peranteau W. Congenital cystic lung lesions: Redefining the natural distribution of subtypes and assessing the risk of malignancy. American Journal of Surgical Pathology. 2019 Jan 1;43(1):47–55.
21. Herrero Y, Pinilla I, Torres I, Nistal M, Pardo M, Gómez N. Cystic adenomatoid malformation of the lung presenting in adulthood. Annals of Thoracic Surgery. 2005 Jan;79(1):326–9.
22. Sousa V, Carvalho L. Congenital cystic adenomatoid malformation of the lung or congenital pulmonary airway malformation. Revista Portuguesa de Pneumologia. 2003;9(3):249–56.

23. Enuh HA, Arsura EL, Cohen Z, Diaz KT, Nfonoyim JM, Cosentino PJ, et al. A fatal case of congenital pulmonary airway malformation with aspergillosis in an adult. International Medical Case Reports Journal. 2014 Mar 20;7(1):53–6.
24. Yonker LM, Mark EJ, Canapari CA. Aspergilloma in a patient with an occult congenital pulmonary airway malformation. Pediatric Pulmonology. 2012 Mar;47(3):308–10.
25. Saleh MES, Beshir H, Awad G, ElDerie A, Sanad M. Surgical outcomes for pediatric congenital lung malformation: 13 years' experience. Indian Journal of Thoracic and Cardiovascular Surgery. 2020 Nov 1;36(6):608–18.
26. Santosham R, Santosham R, Tirunagari V, Jacob SSK. Adenocarcinoma in situ in type I congenital pulmonary airway malformation. Asian Cardiovascular and Thoracic Annals. 2019 Sep 1;27(7):606–8.
27. Fakler F, Aykutlu U, Brcic L, Eidenhammer S, Thueringer A, Kashofer K, et al. Atypical goblet cell hyperplasia occurs in CPAM 1, 2, and 3, and is a probable precursor lesion for childhood adenocarcinoma. Virchows Archiv. 2020 Jun 1;476(6):843–54.
28. Dusmet M. Adult lung tumours of childhood origin. Seminars in Pediatric Surgery. 2015;24(4):196–200.
29. Koh J, Jung E, Jang SJ, Kim DK, Lee BS, Kim KS, et al. Case of mucinous adenocarcinoma of the lung associated with congenital pulmonary airway malformation in a neonate. Korean Journal of Pediatrics. 2018 Jan 1;61(1):30–4.
30. Li J, Chen GS, Zhang X, Moore L, Cheng H. Congenital cystic adenomatoid malformation with associated mucinous bronchioloalveolar carcinoma in a neonate. Fetal and Pediatric Pathology. 2014;33(1):29–34.
31. Singh G, Coffey A, Neely R, Lambert D, Sonett J, Borczuk AC, et al. Pulmonary Kirsten Rat Sarcoma Virus Mutation Positive Mucinous Adenocarcinoma Arising in a Congenital Pulmonary Airway Malformation, Mixed Type 1 and 2. Annals of Thoracic Surgery. 2016 Oct 1;102(4):e335–7.