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Adult lung tumours of childhood origin

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ABSTRACT

The remit of this article is principally to explore the risk of malignancy developing in a congenital cystic adenomatoid malformation (CCAM) in adulthood.

Congenital cystic adenomatoid malformation

CCAMs are congenital cystic lesions—as will be seen the distinction between congenital and acquired lesions can be quite important. They have also been called congenital pulmonary airway malformations (CPAMs).[1] This new name reflects their classification and origin. The term CCAM was coined by Chin and Tang[2] in 1949 to describe the abnormality found in an infant's left lower lobe. This lobe was increased in size and weight and comprised abnormal looking bronchioles, alveolar ducts and alveoli lined with cuboidal epithelium, which gave the tissue a gland-like or "adenomatoid" appearance (Fig 1).

In 1977, Stocker et al.[3] described 3 groups of adenomatoid malformations based on the observations from 35 cases. This classification was updated and expanded in 2002[1] and is fully described in the previous article of this journal.

	Incidence	Gross appearance	Microscopy	Other features
0	1–3%	Solid, the lungs are small and firm throughout	Bronchial airways with cartilage, smooth muscle and glands separated by abundant mesenchymal tissue	Neonates Other malformations Poor prognosis
1	60–70%		The cysts are lined by	Presentation may be late.
				Large cysts (up to 10 cm)
			pseudostratified ciliated cells that are often interspersed with rows of mucous cells	Resectable. Good prognosis. Rarely show carcinomatous change
2	10–15%	Sponge-like multiple small cysts (< 2 cm) and solid pale tumour-like tissue	The cysts resemble dilated bronchioles separated by normal alveoli striated muscle in 5%	Neonates Other malformations Poor prognosis
3	5%	Solid	Excess of bronchiolar structures separated by small air spaces with cuboidal lining (foetal lung)	Neonates Poor prognosis
4	15%	Large cysts (up to 10 cm)	The cysts are lined by a flattened epithelium resting upon loose mesenchymal tissue	Neonates and infants Good prognosis

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The association between type 1 CCAM and adenocarcinoma

Type 1 and type 4 CCAMs account for 70–80% of all CCAMs and are the 2 types that have large cysts. Type 1 CCAMs can be associated with cancer. (In the literature on CCAMs, these are most commonly referred to as bronchioloalveolar carcinoma—BAC; these are now called adenocarcinoma in situ, minimally invasive adenocarcinoma and lepidic predominant invasive adenocarcinoma.[4] For purposes of simplicity, these will henceforth be referred to as low-grade adenocarcinoma throughout this text.) Type 4 CCAMs present a diagnostic challenge, as they can be confused with type I PPB.

Low-grade adenocarcinoma has been reported in type 1 CCAMs.[1,5–13] The age at which these have occurred ranges from 6 months to 63 years old. The true incidence of low-grade adenocarcinoma in CCAMs is difficult to determine. Most publications are case reports or small series. Our institution published a series in 2003,[5] but this certainly would tend to lead to an overestimation of the true incidence as we are a tertiary referral centre for thoracic surgery and our lead pathologists (Prof. Bryan Corrin and Prof. Andrew Nicholson) are national and international experts on pulmonary pathology and are thus referred cases for opinion from afar. The best estimate of the incidence of adenocarcinoma in type 1 CCAM is around 1% (8; Prof. Andrew Nicholson, personal communication).

As described above, there can be clusters of mucogenic cells in type 1 CCAMs. Lantuejoul et al.[14] studied 7 cases of type 1 CCAM with a spectrum of mucinous proliferation ranging from intracystic mucinous cell clusters ($n = 6$) to extracystic mucinous proliferation ($n = 3$) and low-grade adenocarcinoma ($n = 4$). K-*ras* mutations at codon 12 were detected in 3/3 intracystic mucinous cell clusters, in 2/3 extracystic mucinous proliferations and in 3/4 low-grade adenocarcinomas. Furthermore, loss of heterozygosity (LOH) at $p16^{INK4}$ locus with microsatellite alterations was demonstrated in 2/3 intracystic mucinous cell clusters, in 2/3 extracystic mucinous proliferations and in all low-grade adenocarcinomas. In 2 cases of extracystic mucinous proliferation, LOH at the fragile histidine triad (FHIT) gene and the Rb loci were seen. These alterations are highly suggestive that the intracystic clusters of mucinous cells can be precursors to the low-grade adenocarcinomas seen in association with type 1 CCAMs. No EGFR mutations were seen, nor was P53 accumulation. K-*ras* mutations in low-grade adenocarcinoma associated with type 1 CCAM has been described by other authors.[8]

Similarly, foci of atypical adenomatous hyperplasia (AAH) have been described in association with type 1 CCAMs,[7] and these are thought to be possible precursor lesions of low-grade adenocarcinomas, which themselves can progress to become invasive (and metastatic) adenocarcinoma (Figs 2,3).

The majority of low-grade adenocarcinomas associated with type 1 CCAMs behave in a benign fashion—complete resection appears to be curative in the majority of patients. The indolent nature of this disease process is illustrated in a case where the patient underwent curative resection (via left lower lobectomy) of a low-grade adenocarcinoma. Eleven years previously, a biopsy had been taken from the same lobe at the time of the surgical drainage of an empyema and retrospective review of the original biopsy specimen showed low-grade adenocarcinoma.[15] However, this favourable view of the prognosis of low-grade adenocarcinoma associated with type 1 CCAMs must be tempered by 2 facts/findings. The first is that the clinical follow-up of many of the reported cases is relatively short and the second is that there are reports of multi-focal (or synchronous) lesions[12] and metastatic lesions.[6,11,13]

The distinction between type 4 CCAM and pleuropulmonary blastoma

PPB is the most common primary malignancy of the lungs in childhood.[16] Nonetheless, these remain uncommon tumours. There is an international registry for these tumours and a report on 350 cases from this registry has been published quite recently (Messenger). This citation encompasses multiple publications from this group, and the reader can refer to their references for more detail of some of the following information. There are 3 distinct types or stages of these lesions: type I lesions are purely cystic lesions. The interface between the lesion and the surrounding lung is usually abrupt. Within the septa of the lesion, there is a layer of small immature cells with or without rhabomyoblastic differentiation beneath the low cuboidal epithelial cells. The immature cells have a cambium layer-like appearance and can present either as a continuous ribbon of sub-epithelial cells or as discontinuous foci. Microscopic thickening or expansion or the septa by foci of embryonal rhabdomyosarcoma or spindle cell or fibrosarcoma-like areas is still within the spectrum of type I PPB.[16] There is a subset of type I PPB that does not have these primitive small cells/rhabdomyoblasts. These are called regressed or non-progressed type I PPB (Ir PPB).[16] Type II lesions are part solid and part cystic. Type III lesions are solid. The solid parts of these lesions consist of an amalgam of primitive sarcomatous patterns (including embryonal rhabdomyosarcoma, spindle cell or fibrosarcoma-like areas) and blastemal islands surrounded by primitive mesenchyme, cartilaginous nodules with foetal to sarcomatous features and anaplastic cell with large, bizarre nuclei and atypical mitotic figures. These findings explain why histology is of paramount importance in the correct diagnosis of a type I PPB, as opposed to a type 1 CCAM, which cannot be made on clinical grounds in the absence of a history that is suggestive of a PPB (Fig 4).

The majority (2/3) of patients with a PPB have *DICIRI* mutations. This frequency is the same for all 3 types of PPB. Furthermore, the clinical behaviour is identical in patients with or without the mutation, but it is possible that there are other mutations that are similar in effect.[16] This genetic background is the likely explanation for the association of either a family history for PPB or the association with cystic nephroma, ovarian Sertoli–Leydig cell tumours, ciliary body medulloepithelioma, nodular hyperplasia and differentiated carcinoma of the thyroid gland, pituitary blastoma, pineoblastoma, nasal chondromesenchymal hamartoma and embryonal rhabdomyosarcoma.[16,17]

There is a clear progression from type I to type II to type III lesions. Firstly, age at diagnosis is clearly different between the 3. A full 97% of type I lesions are diagnosed before the age of 3 years, the majority are diagnosed within the first year of life; the median age at diagnosis was 8 months. The age at diagnosis is considerably higher for types II and III (at a median of 35 and 41 months, respectively). Conversely, only 1 patient with a higher-grade lesion was under the age of 1 year at the time of diagnosis. The exception to this rule are the type Ir lesions—these can be found for example in relatives of patients with PPB.[16]

Metastases are virtually unknown in type I lesions. The sites of predilection for metastatic lesions in the type II and III lesions are the brain, the bone and, rarely, the liver. However, the presence of metastases at the time of diagnosis is a clear negative prognostic indicator.[16]

Surgery is the cornerstone of treatment for type I lesions and there does not seem to be a clear benefit from adjuvant chemotherapy. On the other hand, surgery and chemotherapy are required in the treatment of type II and III lesions. In these cases, additional radiotherapy is of no proven benefit.[16]