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The argument for operative approach to asymptomatic lung lesions

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ABSTRACT

Antenatal detection of congenital pulmonary airway malformations (CPAM) has improved immeasurably from its initial application in the 1980s and probably encompasses > 80% of all such lesions. Accurate diagnosis still remains less reliable and definitive diagnosis requires detailed anatomical imaging (typically with CT scan) in the post-natal period. About 10% of all lesions will present with symptoms during the neonatal period and the choice of surgical intervention is then easy. For those that remain asymptomatic then there is still a degree of controversy about elective surgical resection. This article presents the case for elective surgery within the first year of life and aims to quantify the risks of non-intervention such as abscess, empyema, recurrent pneumonia, air-leak, and pneumothorax and various types of malignancy in such cases. The current surgical approach now includes both open muscle-sparing thoracotomy and thoracoscopic resection.

Introduction

The terms congenital thoracic malformations (CTM) or congenital pulmonary airway malformations (CPAM) are useful encompassing phrases for congenital developmental lesions derived from lung and its adnexal tissue although neither confers any actual specific histological meaning. These might include parenchymal lesions such as congenital cystic adenomatoid malformation (CCAM), extra- and intra-bronchopulmonary sequestration (BPS), and congenital lobar and segmental emphysemas together with less common entities such as foregut duplication and bronchogenic cysts. Antenatal detection of such lesions has improved immeasurably from initial application in the 1980s, though accurate diagnosis remains less reliable and a definite diagnosis in most cases can only be reached after histological examination of the resected lesion.

The treatment of symptomatic congenital lung lesions is straightforward with resection of the offending lesion. However, the asymptomatic lesion poses a dilemma to the treating clinician (Figure 1) and the aim of this review is to put forward the reasons justifying operative intervention in the majority (although not all) of such infants.

Incidence of CCAM—the scale of the problem

The European Surveillance of Congenital Anomalies (EUROCAT) is an organisation established in 1979 with the aim pulling together disparate national registries on various congenital anomalies. It has been estimated that data from 20 European countries is captured and represents almost 30% of Europe's birth population. The EUROCAT database showed that in the 5-year period (2008–2012), there were 552 fetuses with a “diagnosis” of CCAM (ICD10 Q3380), of which 469 (85%) resulted in a live-birth. There had been 7 who died during fetal life and 76 who were terminated. The prevalence was calculated at 0.81/10,000 fetuses.[1]

Histological/molecular concern

CPAM, although superficially heterogeneous in appearance may share a common embryological origin. The unifying hypothesis proposed by Langston suggested that CPAM can be attributed to variations in airway obstruction *in utero* and that the level, timing and the completeness of the obstruction produce different patterns of malformation.[2] CCAM appear to be derived from the proliferation of peripheral bronchiolar tissue at the expense of alveolar tissues while congenital segmental emphysema (CSE) or peripheral bronchial atresia causes distal air-trapping and the formation of a mucocele from the obstructed airway[3] (Figure 2).

Abbreviations: CTM, congenital thoracic malformation; CPAM, congenital pulmonary airway malformation; CCAM, congenital cystic adenomatoid malformation; CSE, congenital segmental emphysema; BPS, bronchopulmonary sequestration; ILS, intralobar sequestration; ELS, extralobar sequestration; VEGF (R1 and R2), vascular endothelial growth factor (receptors 1 and 2); VAT, video-assisted thoracoscopy; EUROCAT, European Surveillance of Congenital Anomalies (historically actually “European Concerted Action on Congenital Anomalies and Twins”).

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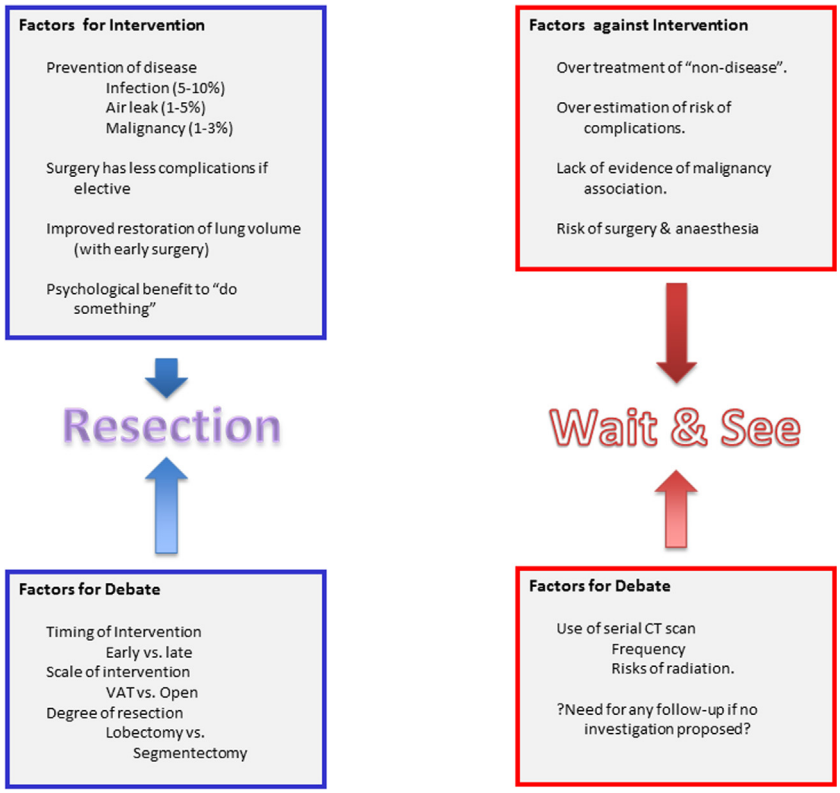

Fig. 1. Decision dichotomy in asymptomatic CPAM.

BPS are from supernumerary lung buds arising caudal to the main lung buds off the primitive foregut. These then continue to migrate caudally with the oesophagus. If these supernumerary lung buds arise before the main lung buds it can be incorporated into the lung pleura making it an intralobar sequestration, if they form after the main lung buds, these will be invested in its own pleura making it an extralobar sequestration (ELS).

A number of recent studies exploring the molecular biology of CPAM have shown clear differences in their cellular heritage and behaviour emphasising that this is not simply normal lung parenchyma which happens to have cystic or solid change within and may explain the predisposition to malignancy later in life.

Expression of HoxB-5 changes during human lung development and parallels that of the mouse. Normally there are high HoxB-5 protein levels in the pseudoglandular phase, with diminution in the canalicular phase and ultimately negligible levels during the alveolar period. Volpe et al.[4] have shown that there are abnormally increased levels of HoxB5 in both mature BPS and CCAM suggesting recapitulation or arrested development of an earlier phase. This is accompanied by alterations in integrin cytoplasmic signalling and aberrant cell adhesion molecule expression (e.g., ICAM and VCAM).[5] Similarly, a small clinical study[6] showed increasing expression of the VEGF receptor (VEGFR2) from controls to CCAM and from CCAM to BPS although actual levels of VEGF and its other receptor were not dissimilar.

Cass et al.[7] from Philadelphia looked at the balance between cell proliferation and apoptosis in CCAM specimens resected both before and after birth. Overall, these showed a significant twofold increase in the cell proliferation index Ki-67 and a fivefold decrease in apoptotic bodies compared with age-matched normal lung tissue. Furthermore those resected during fetal life had the highest rates of Ki-67 expression.

Finally, we reported a histological review of 31 resected CPAM specimens focussing particularly on striated muscle.[8] Specimens were conventionally stained using phosphotungstic acid and immunostained for myoglobin and desmin. Striated muscle cells were identified diffusely or as a focal proliferation in 5 (16%) patients. Underlying lung anomalies included an intra-abdominal pulmonary sequestration, intrathoracic sequestration ($n = 2$) and 2 Stocker type II intrathoracic CCAMs. Striated muscle cells are not a normal constituent of lung parenchyma and presumptively may be the starting point for the development of so-called rhabdomyosarcoma (now PPB).

Finally, on this background of inherent biological activity an active inflammatory process is added post-natally, presumably caused by respiratory microflora and impaired mucosal defences. Pellizo et al.[9] identified a chronic inflammatory picture in 79% of their resected CCAM specimens.

Natural history of congenital thoracic malformation

Most lesions are now detected on the antenatal ultrasound scan, performed typically at 18–20 weeks gestation and before any kind of detrimental impact on the fetus has become apparent. Thereafter a small proportion ($< 5\%$) will go on to cause fetal cardiac failure and hydrops leading to demise and/or severe maternal mirror syndrome.[10] These are invariably the larger lesions and effects can be predicted by serial monitoring of size and mediastinal shift, supplemented by fetal MR scanning. At this stage, there are therapeutic options available particularly for the macrocystic lesions including thoracoamniotic shunting, application of laser energy percutaneously, and fetal lung resection.[10–14] Up to 20% will be delivered and then be subject to respiratory distress in the first days and weeks of life with the need for usually open thoracotomy and lobar/lesion resection.[15]

The key group however, and certainly the most controversial, are those antenatally detected who remain to all intents and purposes asymptomatic (Figures 3 and 4). Firstly it is worth re-emphasising that fetal detection is just that detection. It is not an