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Prenatal diagnosis of echogenic lung: evolution and outcome

S. ILLANES*, A. HUNTER*, M. EVANS†, E. CUSICK‡ and P. SOOTHILL*

**Fetal Medicine Research Unit, Obstetrics and Gynaecology, Clinical Sciences South Bristol, University of Bristol, †Department of Paediatric Pathology, St Michael's Hospital, ‡Department of Paediatric Surgery, Bristol Royal Hospital for Children, Bristol, UK*

KEYWORDS: CCAM; fetal; hydrops; prognosis

ABSTRACT

Objectives *Despite the feasibility of detecting lung lesions by antenatal ultrasound, there are problems in correlating the prenatal diagnosis with the final histology and in predicting the outcome. In order to better describe these factors, we reviewed the outcome of fetuses that had been diagnosed with echogenic lung in a referral fetal medicine unit.*

Methods *We searched the database of a tertiary fetal medicine unit for all cases of fetal echogenic lung seen since 1994 and studied the maternal and neonatal records found.*

Results *There were 48 cases of echogenic lung diagnosed at a median gestational age of 21 (range, 19–29) weeks, including 43 (90%) cases of congenital cystic adenomatoid malformation (CCAM) and 5 (10%) of pulmonary sequestration (PS). The evolution of the fetal abnormality after diagnosis was: in 22 (45.8%) cases the lesion disappeared; in 17 (35.5%) cases the lesion remained stable and six (12.5%) cases became severe. Three (6%) women underwent termination of pregnancy. The lesions were equally distributed between the two sides of the thorax. Mediastinal shift was associated with a threefold increase in the possibility of clinical deterioration (17% vs. 5%), and the disappearance of the lesion was twice as likely to occur when the lesion was classified as microcystic as when it was macrocystic (67% vs. 36%). Features of hydrops were found in 9 (21%) fetuses and in six (13%) cases progressed and resulted in intrauterine or neonatal death. Sixty-four percent of cases with lesions that disappeared during the pregnancy had an abnormal computed tomography (CT) scan, and the prenatal diagnosis correlated with histology in 36% of these cases. Of the cases in which the lesions remained stable, 70.5% had an abnormal CT scan and the prenatal diagnosis correlated with the histology in 67% of the cases.*

Conclusions *Prenatally diagnosed echogenic lung has a good prognosis in the absence of hydrops. The ability to correctly assess echogenic lung lesions and the need for surgery by prenatal ultrasound is limited. Copyright © 2005 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Prenatal diagnosis of lung malformations relies on the recognition of increased echogenicity and/or cysts in the thoracic cavity by high-resolution ultrasound during the second trimester. These findings are commonly associated with one of the following lesions: pulmonary sequestration (PS); congenital cystic adenomatoid malformation (CCAM); and less frequently, tracheal obstruction, bronchial atresia or congenital lobar emphysema[1,2]. The natural history of the two most common pathologies (PS and CCAM) varies and may be associated with the development of hydrops or may involve lesions that remain stable in size as the pregnancy progresses or that decrease or even disappear[3,4]. Fetal hydrops may be present if the intrathoracic pressure is high enough to impair venous return to the heart[5,6] and polyhydramnios can occur if this compresses the esophagus, thus impairing fetal swallowing[7]. Nevertheless, when diagnosed antenatally, the outcome of these pregnancies is usually good even when there is significant mediastinal shift or lung compression, and many lesions decrease in size or even disappear[1,4,8,9]. When lesions are no longer seen on ultrasound, it is possible that the initial diagnosis was wrong or that the lesion is still present but too small to detect. Therefore, postnatal investigations such as chest X-ray or computed tomography (CT) are recommended in all infants born with a prenatal diagnosis of lung abnormality[9].

Correspondence to: Dr S. Illanes, Fellow in Fetal Medicine, Fetal Medicine Research Unit, University of Bristol, St Michael's Hospital, Southwell Street, Bristol BS8 4NE, UK (e-mail: s.illanes@bristol.ac.uk)

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If the diagnosis is confirmed postnatally, the current management is surgical resection. Most surgeons recommend this treatment, even if the infant is asymptomatic, to prevent future infection[10]. Although conservative management of asymptomatic lesions has been proposed, in order to avoid surgical and anesthetic complications[10] there is not enough evidence to support this approach.

Despite the feasibility of detecting lung lesions by antenatal ultrasound, there are problems in correlating the prenatal diagnosis with the final histology and in predicting the outcome. Davenport *et al*. have recently published a series showing that antenatal ultrasound characteristics were poorly predictive of the eventual histological classification into CCAM or PS and that a high number of lesions persisted despite antenatal 'disappearance' on scan[9]. Histological reports often show both types of lesion in the same patient[9,11] leading to the possibility that these two pathologies are a continuum of the same disease.

In order to better describe the factors associated with poor outcome and to confirm the findings described above, we conducted a retrospective review of cases of CCAM and PS seen in our unit over a 10-year period. During this time period, we had consistent pregnancy and postnatal management of these conditions, allowing relatively consistent data collection.

METHODS

Computerized records of all fetuses that had undergone ultrasound examination between 1994 and 2003 at the Fetal Medicine Research Unit, St Michael's Hospital, Bristol, UK (the referral unit for the diagnosis and management of congenital malformations in the South West of England), were analyzed for cases of CCAM and PS. In most cases, serial ultrasonography was performed to monitor the development of the lesion(s) and to assess the presence or absence of complications. The progression of the lesion was classified as: (1) severe – if hydrops appeared and progressed or if the lesion increased in size; (2) stable – if the lesion did not increase or decrease in size during the pregnancy but was still present in the last scan before delivery and (3) disappeared – if the lesion was impossible to see on the last scan.

The diagnosis of the lesions was based on the presence of an echogenic mass in the thorax with or without cysts for CCAM and on the presence of an echodense lesion with an even and wedge-shaped appearance for PS. The presence of a systemic arterial blood supply arising from the aorta was looked for, detected by prenatal color flow Doppler, and confirmed the diagnosis of PS. Information recorded for each case included the gestational age at diagnosis, size, laterality, description of lesion, the presence of any other anomaly, hydrops, polyhydramnios, gestational age at birth, mode of delivery and intrauterine death (IUD) or live birth. When an IUD occurred, the pathology records were inspected for confirmation of the abnormality and cause of death. For liveborn infants, the neonatal records were studied and neonatal complications and follow-up investigations such as chest X-ray and CT scan were noted. If surgery was required, the histology of the lesion was checked.

The place of delivery of the infant was decided on the basis of the progression of the disease. If there was worsening of the lesion (the severe category), most infants were delivered in our unit to ensure the availability of rapid access to neonatal intensive care and surgery, but if the lesion remained stable or disappeared, infants were usually born at the referring institutions.

Infants were investigated initially by a chest radiograph and then by an intravenous contrast-enhanced CT scan within 6 months of birth. Surgical excision would have been advised for those infants symptomatic at birth, but none was, or if the radiological study was abnormal in an apparently well infant. All surgical specimens underwent histopathological assessment.

RESULTS

There were 48 cases of echogenic lung diagnosed at a median gestational age of 21 (range, 19–29) weeks. The median age of the mother was 26 years and 48% were primigravidas. The ultrasound prenatal diagnosis was CCAM in 43 (90%) cases and PS in five (10%) cases. The evolution of the fetal abnormality after diagnosis was: in 22 (45.8%) cases the lesion disappeared; in 17 (35.5%) cases the lesion remained stable and six (12.5%) cases became severe. Three women underwent termination of pregnancy (TOP); one of these fetuses had non-immune hydrops and the other two (6.2%) did not (Table 1).

Mediastinal shift at presentation was related to the classification of progression only in CCAM (mediastinal shift was not found in the PS cases). About two thirds (67%) of the CCAM cases had mediastinal shift at diagnosis and when present it was associated with a threefold increase in the possibility of clinical deterioration (17% vs. 5%). When the evolution was compared with respect to the appearance of the CCAM (44% microcystic and 56% macrocystic), the lesion disappeared in twice as many cases when the lesion was microcystic (67% vs. 36%). The lesions were equally distributed between the two sides of the thorax and we did not see any bilateral cases. Features of hydrops were found in nine (19%) fetuses, all of them with prenatal diagnosis of CCAM. One of these nine pregnancies ended in TOP. One case with an initial finding of mild pleural effusion remained

Table 1 Prenatal evolution of echogenic lung

Classification	n	%
Disappeared	22	46
Stable	17	36
Severe	6	12
TOP	3	6

TOP, termination of pregnancy.

stable during the pregnancy and another case had mild pleural and pericardial effusions at 36 weeks following a diagnosis of CCAM made at 20 weeks. The remaining six cases progressed and resulted in intrauterine or neonatal death. None of the cases with an antenatal diagnosis of PS developed features of hydrops. The amniotic fluid volume at diagnosis was normal in 45 (93%) patients, and there was polyhydramnios in two cases and oligohydramnios in one case. Associated abnormalities found on ultrasonography included bilateral choroid plexus cysts (one case), mild ventriculomegaly (one case) and mild hydronephrosis (one case). Subsequently, these all appeared to be of no clinical significance.

Of the 22 lesions that disappeared during the pregnancy, 21 were assessed as being CCAM and one PS, and all these cases were asymptomatic at birth (Figure 1). Two were lost to follow-up and one had not undergone postnatal studies at the time of writing. Data including both chest X-ray and CT were available in all other 19 cases. Five patients (including the case assessed prenatally as PS) had a normal X-ray shortly after birth and normal CT scan at about 6 months of age. Fourteen (64%) of the 22 cases in which the lesion disappeared had an abnormal CT scan, of which only six had an abnormal X-ray at birth. Three with an abnormal CT did not have surgery and were under follow-up at the time of writing. Of the 11 that underwent surgery, the prenatal diagnosis of CCAM was confirmed histologically in only four (36%) cases. The remaining seven diagnoses were either congenital lobar emphysema (three cases), PS (three cases) and one result came back as normal.

Of the 17 lesions that remained stable during pregnancy, 14 were diagnosed as CCAM and three as PS. All were asymptomatic at birth (Figure 2). Three (17.6%) infants, two with prenatal diagnosis of CCAM and one with PS, had normal CT scans in the postnatal evaluation, but one of the diagnosed CCAM had an abnormal X-ray shortly after birth. Twelve (70.5%) cases (10 CCAM and two PS as diagnosed prenatally) had an abnormal CT, and

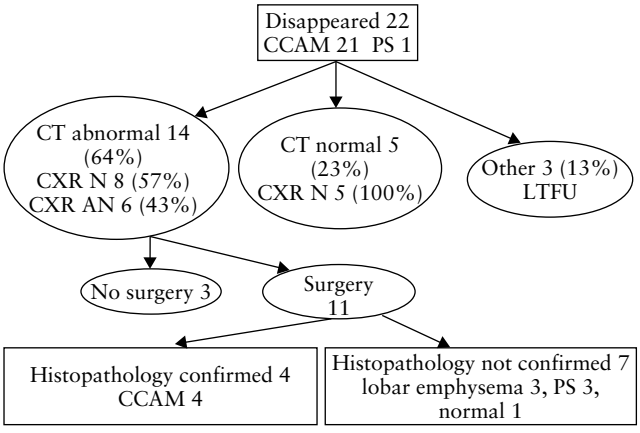

Figure 1 Flow chart of the postnatal evolution of the lesion classified as 'disappeared'. CCAM, congenital cystic adenomatoid malformation; CT, computed tomography; CXR AN, chest X-ray abnormal; CXR N, chest X-ray normal; LTFU, lost to follow-up; PS, pulmonary sequestration.

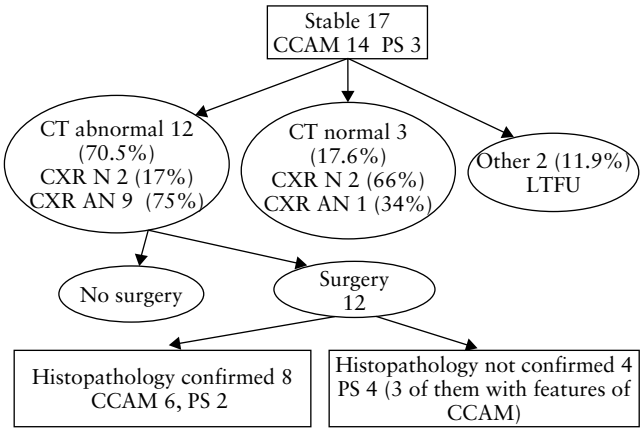

Figure 2 Flow chart of the postnatal evolution of the lesion classified as 'stable'. CCAM, congenital cystic adenomatoid malformation; CT, computed tomography; CXR AN, chest X-ray abnormal; CXR N, chest X-ray normal; LTFU, lost to follow-up; PS, pulmonary sequestration.

the X-ray after birth was also abnormal in nine of these cases. All 12 patients underwent surgery, and the diagnosis was confirmed on histology in six cases of CCAM and in the two cases of PS. The four remaining cases prenatally diagnosed with CCAM had a histological diagnosis of PS (three with features of CCAM). The two prenatal diagnoses of PS were confirmed on the histopathology. Two cases were lost to follow-up.

Of the six lesions that showed a severe course, all had a prenatal diagnosis of CCAM, four had an IUD and two a neonatal death (Table 2). Two of the patients had features of hydrops at diagnosis at 28 and 29 weeks, respectively, and the diagnosis of an IUD was made within a week. One of the other two IUDs had a prenatal diagnosis of CCAM at 20 weeks with the appearance of hydrops at 22 weeks and confirmation of IUD at 26. The other had a diagnosis of CCAM at 20 weeks with development of hydrops at 25 weeks due to the presence of a large cyst in the right thorax. The cyst was drained at 25 weeks but the fluid refilled the cavity and a shunt was placed at 26 weeks. The diagnosis of IUD was made the day after the procedure and the postmortem confirmed a CCAM, pulmonary hypoplasia and hemorrhage of the left lung, which was probably iatrogenic. One of the two cases of neonatal death had a diagnosis of CCAM at 22 weeks, with normal follow-up until 29 weeks when pleural effusions appeared with worsening mediastinal shift and then uterine contractions. An emergency Cesarean section was performed at 30 weeks and a postnatal CT scan showed features of a CCAM with a collapsed left lung. The newborn died at 5 days of age, and although the prenatal diagnosis was CCAM, the postmortem revealed the lesion was a left PS, with pulmonary hypoplasia, bronchopleural fistula, small heart and bilateral pneumothorax. The other case in which neonatal death occurred had a diagnosis of CCAM at 23 weeks with the appearance of hydrops at 27 weeks and a large cyst in the right thorax. A shunt was placed with satisfactory evolution and reversal of the hydrops at 29 weeks. At 30 weeks the patient was

Table 2 Prenatal evolution and outcome of the cases classified as severe

Case	Prenatal diagnosis	GA at diagnosis (weeks)	GA of hydrops (weeks)	Invasive procedure (weeks)	Outcome (weeks)
1	CCAM	28	28	—	IUD 29
2	CCAM	29	29	—	IUD 30
3	CCAM	20	22	—	IUD 26
4	CCAM	20	25	Dr 25, PSh 26	IUD 26
5	CCAM	22	29	—	De 30, DD 5
6	CCAM	23	27	PSh 29	De 30, DD 1

CCAM, congenital cyst adenomatoid malformation; De, delivery; DD, day died; Dr, drainage; GA, gestational age; IUD, intrauterine death; PSh, pleural shunt.

admitted in preterm labor, delivering a newborn of 1412 g who died the same day from pulmonary hypoplasia.

DISCUSSION

Our series of echogenic lung lesions is one of the largest published from a single center and has the advantage that we have served a relatively stable population with unchanged pre- and postnatal management policies for at least 10 years allowing relatively consistent data collection. The median gestational age at diagnosis of 21 weeks is in agreement with other series[9] showing that the vast majority of the echogenic lung lesions that will be detected prenatally are seen at the time of the anomaly scan.

The percentage of women that choose a TOP has fallen over 10 years from between 10% and 33%[4,12,13] to less than 2%[9]. In this study, the percentage was 6.2%, which probably reflects the length of our review (1996 to 2004) and the changes in the counseling for this pathology in accordance with the increasing data concerning the relatively benign evolution.

Mediastinal shift has been considered an important factor in the prognosis by some authors[13]. However, others think that the presence of mediastinal shift at the time of diagnosis is not an indicator of unfavorable outcome[4,14]. In our study, the presence of mediastinal shift at diagnosis was related to a threefold increase in the risk of having a severe evolution. Nevertheless, all the cases in our series that followed a severe evolution also had hydrops making it difficult to determine the influence of mediastinal shift on prognosis independently from other factors.

Classifications of the lesions, on the basis of ultrasound appearance, into macro- and microcystic have been widely used[9,13]. There is a degree of correlation between this classification with the natural history[9] in that macrocystic lesions tend to be more stable, whereas microcystic disease tends to diminish or resolve during pregnancy. This is in contrast to earlier data[13] suggesting a better survival if the CCAM was macrocystic. Our data appear to support the more recent observation as resolution occurred in twice as many cases when the lesion was microcystic.

The association between hydrops fetalis and poor outcome in the presence of an echogenic lung is well-known. There are several publications confirming high rates of intrauterine or neonatal death with hydrops even as high as 100%[4,12]. In our series, the presence of features of hydrops at diagnosis or during follow-up was associated with a mortality of 6/8 (75%). Of the two surviving infants, one had a pleural effusion at the time of diagnosis that remained stable for the rest of the pregnancy, and the other developed hydrops at 36 weeks. Like CCAM, PS can also cause fetal hydrops secondary to a mass effect. However, all our cases of hydrops were related to a diagnosis of CCAM. In spite of the assessment of other prenatal markers, fetal hydrops proved to be the single most useful predictor of fetal death in our study in agreement with the literature[1,4,14], and if present at diagnosis, survival rates are very poor[9].

Echogenic lung lesions are rarely associated with other malformations[12,14], but there are some reports of an association with renal abnormalities, cardiac anomalies and aneuploidy[15–17]. However, because of the low incidence of chromosomal abnormalities, many authors would not recommend karyotyping. Our data also show that the associated malformation rate was not significant and we did not have a single case of aneuploidy. We support the management of not recommending chromosomal investigation unless there are other findings on the prenatal scan.

Following histological examination of the affected lesions, it has become evident in recent years that the ability to correctly assess these lesions by prenatal ultrasound is limited[18]. In particular, antenatal ultrasound characteristics are poorly predictive of the eventual histological classification into CCAM or sequestration[9] but the pathology is not always clear and both types of diagnosis can be seen in the same lesion[9,11]. Conran *et al.* report, in the largest published series, that pulmonary sequestration may contain CCAM in up to 50% of cases, indicating that the occurrence of CCAM within PS is more frequent than previously believed and the presentation of these cases may differ from PS cases without associated CCAM[19]. This has led to the possibility that these two pathologies are parts of a spectrum of the same disease. We found agreement between the prenatal diagnoses of CCAM with the histopathology in about half the cases in accordance with other studies, and thus we suggest caution when predicting the outcome following prenatal scanning. This low prediction may be partially explained by the length of our review (9 years) and the significant changes and improvements that occurred in the imaging technology used to make the diagnosis over this time. On the other hand, we have a good correlation of prenatal diagnosis of PS and histopathology, probably due to the specificity of the diagnosis based on the presence of a systemic arterial blood supply. A new classification system of fetal lung anomalies by two-dimensional and color Doppler ultrasound may further improve our understanding of variability of fetal lung lesions[20]. Moreover, some reports suggest that magnetic resonance

imaging may be a valuable adjunct to ultrasound for prenatal diagnosis and may be helpful in distinguishing PS from CCAM[21].

Although large echogenic lesions diagnosed *in utero* can progress, the natural history is very variable. Adzick *et al*., in a large series of fetal lung lesions, found that although most PS lesions shrank dramatically before birth, only 15% of CCAM decreased in size during pregnancy[12]. Other authors have reported spontaneous regression of the mass in more than half of CCAM cases[22]. Nearly half of our cases 'resolved' *in utero* and this may reflect a stable population where all the cases with the diagnosis of echogenic lung detected were referred to our unit, allowing good follow-up of the more benign cases. In the cases in which the lesions remained stable and were still present in the last prenatal scan, around 15% had normal postnatal CT. This finding differs from other published series when a normal CT after antenatally diagnosed lesions was exceptional[9,23]. However, the apparent *in-utero* disappearance is not necessarily a true spontaneous resolution, and many series report a subsequent abnormal CT scan[9,12,18]. Our finding of an abnormal CT in over 60% of this group of patients supports the need for postnatal CT for all infants with an antenatal history of prenatal echogenic lungs on ultrasound examination despite being both asymptomatic and having a normal X-ray at birth.

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