Mainstem bronchial atresia: a lethal anomaly amenable to fetal surgical treatment

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ABSTRACT

Purpose: The purpose of this study was to review the unique imaging characteristics, prenatal course, and outcomes for fetuses with mainstem bronchial atresia (MBA).

Methods: The records of all patients referred for a fetal lung malformation from 2001 to 2012 and the medical literature were reviewed to identify cases of MBA.

Results: Of 129 fetuses evaluated, 3 were diagnosed prenatally with right-sided MBA. The first had a CCAM-volume ratio (CVR) of 9, hydrops, mirror syndrome, and preterm delivery of a nonviable fetus. The second (CVR 2.6) had ascites, preterm delivery at 34-weeks, and neonatal demise. The third fetus (CVR 5.7) presented with hydrops at 21-weeks, prompting fetal pneumonectomy. Postoperatively, hydrops resolved, and the contralateral lung grew dramatically, but preterm delivery occurred 3 weeks later. Ventilation could not be sustained, and the infant died. Four similar cases of MBA were in the literature, all right-sided. Two fetuses with hydrops delivered at 25-weeks and died immediately. One pregnancy was terminated. One fetus underwent pneumonectomy at 24-weeks but died intraoperatively.

Conclusion: MBA is a rare and lethal lesion that must be distinguished from other right-sided lung masses. Fetal pneumonectomy can be performed with resolution of hydrops and compensatory contralateral lung growth, but remains limited by complications of preterm birth.

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Mainstem bronchial atresia (MBA) is a rare and likely under-recognized, congenital malformation of the pulmonary architecture that remains incompatible with life. Unlike lobar or segmental bronchial atresia, MBA has a dramatic perinatal course characterized by marked overdistention and malformation of the right lung, mediastinal compression with contralateral shift, hydrops, mirror syndrome, and ultimately fatal or neonatal demise [1,2]. The lethal outcomes in this condition have prompted consideration of fetal surgical intervention as a potential means of fetal salvage, but to date, no successful outcomes are reported. The purpose of this study is to report 3 cases of prenatally diagnosed MBA, including one that was treated with open fetal pneumonectomy, and to discuss the keys to diagnosis and treatment of this uncommon entity.

1. Methods

With approval from the Institutional Review Board of Baylor College of Medicine (H-29695), the records of all patients referred to our comprehensive fetal treatment center for a fetal lung malformation from 2001 to 2012 were reviewed. MEDLINE®/PubMed® database searches were conducted in an iterative manner during January–March 2013 to retrieve articles related to the prenatal diagnoses of fetal lung masses with an emphasis on mainstem bronchial atresia over a 30 year period from January 1982 to January 2012. Search terms were restricted to the English language and included “congenital lung malformation”, “congenital cystic adenomatoid malformation”, “CCAM”, “bronchial atresia”, “mainstem bronchial atresia”, “prenatal diagnosis”, “fetal surgery”, and “fetal intervention.” No specific key words were required as inclusion criteria since a relatively small number of studies existed on the topic, so a “bottom-up” search strategy was required.

2. Results

Of 129 fetuses evaluated for a fetal lung malformation at our center, three (2.3%) were diagnosed prenatally with MBA. All cases were male and showed large, right-sided masses with dilated right mainstem bronchi on fetal MRI. Mortality in these cases was 100%.
2.1. Case reports

2.1.1. Patient 1

A 32-year primigravida presented to the Texas Children’s Fetal Center for evaluation of a right-sided lung mass detected on routine ultrasound at 19 weeks’ gestation. The pregnancy was conceived without assistance and had been progressing uneventfully until that point, and several first trimester ultrasounds had been normal. Evaluation with fetal MRI at 22 3/7 weeks showed an extremely large, right-sided mass with marked contralateral mediastinal shift, eversion of the right hemidiaphragm, and a very small left lung. A cystic lesion was noted centrally, suggestive of a mucocele proximal to a centrally obstructed bronchus (right main; Fig. 1). The CCAM-volume ratio (CVR) was measured at 9. No normal right lung was visualized and the presumptive diagnosis was proximal right bronchial atresia. The mother received steroids in an attempt to limit growth of the fetal mass and possibly to enhance maturation of the normal, contralateral lung. Over the next several weeks the fetal hydrops progressed to maternal mirror syndrome, leading to an induced vaginal delivery of a hydropic, nonviable fetus at 29-6/7 weeks’ gestation. The postmortem examination revealed atresia of the right mainstem bronchus with marked dilation of the distal, obstructed airways.

2.1.2. Patient 2

A 16 year-old primigravida was evaluated at 18 weeks gestation for sonographic evidence of an echogenic right chest mass. Fetal MRI at 21-2/7 weeks’ gestation, revealed a large, right-sided, homogenous mass occupying the entire right hemithorax and causing eversion of the hemidiaphragm, significant mediastinal shift, compression of the left lung, and ascites (Fig. 2A). The CVR was 2.6; there was no hydrops. The mother was given steroids, and the pregnancy continued without significant changes. Repeat fetal MRI at 32-1/7 weeks GA revealed a slight decrease in the size of the central cystic lesion (dilated bronchus), from 15 × 12 × 13 mm to 14 × 9 × 12 mm, and improvement in the diaphragmatic eversion. However, the leftward mediastinal shift and left lung hypoplasia remained significant (Fig. 2B–D).

The fetus was delivered at 34 weeks, intubated, and quickly required escalation of respiratory support to include high frequency oscillatory ventilation and nitric oxide therapy. Initial chest x-rays revealed a partially air-filled lung on the left side. The patient had progressive failure of ventilation despite maximum support, and was not considered a candidate for ECMO because of irreversible, severe pulmonary hypoplasia. An urgent right thoracotomy was done with the goal to decompress the mass-effect, and to consider right pneumonectomy. During operation, the neonate’s respiratory status continued to decline. Given the poor prognosis, the operation was ended without resection. The infant died shortly after support was withdrawn. Postmortem examination confirmed the diagnosis of right mainstem bronchial atresia with a 2 mm atretic segment near the lung hilum. There was massive hyperplasia of the right lung (observed weight of right lung = 56.5 g; expected weight of both lungs combined = 33.5 g) and marked distention of the obstructed bronchi, mild bronchiectasis and bronchiolectasis, and patchy fluid-filled air spaces with double capillary alveolar walls. The right hemithorax was expanded with shift of the mediastinum into the left hemithorax causing posterior displacement of the left lung. The left lung was severely hypoplastic (observed weight = 8.7 g; expected weight = 33.5 g for combined right and left lungs).

2.1.3. Patient 3

A 35 year-old G6P4 woman with a history of 4 prior cesarean sections and gastric bypass was referred after fetal ultrasound at 19 5/7 weeks’ gestation showed a right lung mass. Fetal center evaluation, including fetal MRI, at 20-6/7 weeks’ gestation, showed evidence for right mainstem bronchial atresia. The entire right lung was massively over expanded (occupying 80% of the thorax) with compression of the right hemidiaphragm, no normal appearing right lung tissue, and a CVR of 5.7 (Fig. 3A and B). The fetus had findings of hydrops with abdominal ascites, scalp edema, and a small pericardial effusion. Echocardiogram revealed compression of the cardiac chambers and signs of early heart dysfunction, including atrioventricular valve regurgitation, flow reversal in the ductus venosus, and notching in the umbilical vein. After extensive multidisciplinary consultation, discussion of treatment options, and review of the case by the Fetal Therapy Board at Texas Children’s Hospital and Baylor College of Medicine, the family asked to proceed with efforts at fetal surgical resection, understanding that the approach was reasonable but that the outcome of this intervention could not be predicted. Open fetal surgery was performed at 21 weeks. Following extensive lysis of adhesions, uterine exposure was achieved and a stapled hysterotomy performed. The right arm of the fetus was delivered and right chest exposed. Given the tamponade physiology, a 20 cc/kg bolus of 5% albumin was administered in the umbilical vein to preload the heart, and then a right thoracotomy was performed. Efforts were taken to exteriorize the right lung mass slowly to minimize abrupt changes in mediastinal pressure. Expected fetal bradycardia was treated with atropine and low dose ephedrine. Examination of the thoracic anatomy confirmed massive over inflation of all three lobes of the right

Fig. 1. T2-weighted fetal MR single shot imaging with additional bFFE images of a 22-3/7 weeks GA fetus. Sagittal (A) and axial (A) views demonstrate an extremely large, right side based chest mass with marked mass effect, including displacement of the heart and mediastinum, and inversion of the hemidiaphragms, and very little lung tissue visible on the left. There is a central high signal branching structure at the right hilum that is very suggestive of a mucocele and central bronchial atresia of the right lung. Measured CVR = 9.
lung and marked distention of visible airways. Overdistention of the lung parenchyma limited exposure of the right lung hilum, and in this setting a surgical repair of the obstructed bronchus was not possible. A right pneumonectomy was performed using a TA-30 stapler. Following resection and fetal resuscitation using echocardiographic-guided volume and inotrope administration, the cardiac function improved. The uterus was closed and the mother recovered without event over the next 5 days. At this point there was a normal cervical length and no sign of labor and the mother was treated with prophylactic tocolytic medications. Fetal hydrops resolved over the first 10 postoperative days, and repeat ultrasound showed a gradual increase in left lung size (Fig. 3C and D). Over the next week, however, the cervical length began to shorten and on postoperative day 18, the mother developed acute onset lower abdominal pain, tenderness and vaginal bleeding. Concern for placental abruption and uterine rupture prompted an urgent exploratory laparotomy. At operation, the hysterotomy was intact. The uterus was found to have adhesions anteriorly that seemed to tether the bladder, thought the cause of pain. The adhesions were lysed and abdomen closed. On post fetal resection day 20, the patient progressed to labor and was taken for urgent cesarean delivery, but a precipitous vaginal birth ensued with delivery of a 520 g infant. Apgars were 1, 1 and 2 at 1, 5 and 10 minutes, respectively. The infant was intubated and supported with mechanical ventilation. Although oxygen saturation reached 94% and stayed in the 70–80% range, ventilation remained poor with pCO2 consistently >100. The infant remained acidotic and died at just over 4 hours of age. Pathologic examination of the resected lung specimen revealed a grossly enlarged right lung (observed right lung weight = 41 g; expected weight of both lungs combined = 9.6 g) with mildly dilated lobar bronchi, consistent with the impression of right mainstem bronchial atresia. Histologically, the lung showed maldevelopment with features of cystic adenomatoid malformation, type 2. Examination of the placenta revealed no definitive amnion nodosum and no features of amnion separation. There were microscopic findings of a severe fetal inflammatory response in the vessels of the placenta and there were features of an ascending infection, which ultimately was deemed a possible cause of premature rupture of membranes. The thoracotomy incision was well-healed and the site of the right pneumonectomy was intact. There was no evidence of infection within the prior surgical site.

2.2. Review of the literature

After extensive review of the literature, only two studies were identified that described a total of 4 cases of MBA (Table 1). Keswani and colleagues reported two cases in 2005 [1]. The first presented at 18 weeks with a large right-sided lung mass. Fetal hydrops was seen at 19 2/7 weeks (mild ascites and scalp edema). Following maternal steroids the signs of hydrops were thought to improve, but by 22 weeks the hydrops had worsened. Fetal MRI suggested atresia of the right bronchus. By 25 weeks, the mother had developed polyhydramnios and mirror syndrome leading to an induced vaginal delivery at 29 weeks. The second case presented at 16 weeks with a large right-sided lung mass. Fetal hydrops was seen at 18 weeks (mild ascites and scalp edema). Following maternal steroids the signs of hydrops were thought to improve, but by 22 weeks the hydrops had worsened. Fetal MRI suggested atresia of the right bronchus. By 25 weeks, the mother had developed polyhydramnios and mirror syndrome leading to an induced vaginal delivery at 29 weeks.
birth at 25 3/7 weeks of a grossly hydropic, nonviable fetus. Autopsy revealed right mainstem bronchial atresia with an enlarged tri-lobed lung weighing 29.2 g. The second patient of this report presented at 16 weeks’ gestation with a large echogenic mass in the right chest, initially diagnosed as a type III CCAM. On 18 week fetal MRI the CVR was 0.68 and there was contralateral mediastinal shift with a small

Table 1

<table>
<thead>
<tr>
<th>Series</th>
<th>Prenatal diagnosis</th>
<th>Prenatal imaging</th>
<th>Fetal hydrops</th>
<th>Prenatal therapy</th>
<th>Outcome</th>
<th>Postmortem diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keswani, 2005</td>
<td>R MBA</td>
<td>Fetal MRI</td>
<td>Yes</td>
<td>Maternal steroids</td>
<td>Mirror syndrome, labor induction, nonviable fetus, 25 wks GA</td>
<td>Bronchial atresia at origin of right mainstem</td>
</tr>
<tr>
<td>Keswani, 2005</td>
<td>R MBA</td>
<td>Fetal MRI</td>
<td>Yes</td>
<td>Fetal pneumonectomy, 24 wks GA</td>
<td>Intraoperative fetal demise</td>
<td>Atresia of right hilar bronchus</td>
</tr>
<tr>
<td>Abitayeh, 2010</td>
<td>Type III CCAM</td>
<td>3-D US</td>
<td>Yes</td>
<td>Fetal thoracoamniotic shunt, 23 wks GA</td>
<td>Premature delivery, 25 wks GA; neonatal demise</td>
<td>Right mainstem bronchus atresia</td>
</tr>
<tr>
<td>Abitayeh, 2010</td>
<td>Probable R MBA</td>
<td>3-D US</td>
<td>Yes</td>
<td>None</td>
<td>Elective TOP, 22 wks GA</td>
<td>Distal right Mainstem bronchus atresia</td>
</tr>
<tr>
<td>Case 1</td>
<td>R MBA</td>
<td>Fetal MRI</td>
<td>Yes</td>
<td>Maternal steroids</td>
<td>Mirror syndrome, preterm delivery of nonviable fetus, 29 wks.</td>
<td>Short atresia and bronchomalacia of right mainstem bronchus</td>
</tr>
<tr>
<td>Case 2</td>
<td>R MBA</td>
<td>Fetal MRI</td>
<td>No</td>
<td>Maternal steroids</td>
<td>Premature birth, 34 wks, neonatal demise</td>
<td>Right mainstem bronchus atresia</td>
</tr>
<tr>
<td>Case 3</td>
<td>R MBA</td>
<td>Fetal MRI</td>
<td>Yes</td>
<td>Fetal Pneumonectomy, 21 wks GA</td>
<td>Premature birth, 24 wks, neonatal demise</td>
<td>Right mainstem bronchus atresia</td>
</tr>
</tbody>
</table>

Abbreviations: R – right; MBA – mainstem bronchial atresia; weeks – wks; US – ultrasound; TOP – termination of pregnancy; GA – gestational age.
pericardial effusion. The patient was monitored closely over the next several weeks, and by 22 weeks' gestation the fetal MRI demonstrated distinct radiographic features common to all these cases: a) a markedly enlarged right-sided lung lesion, b) eversion of the right hemidiaphragm, c) mediastinal compression and d) ascites. The mass continued to grow rapidly and at 24 weeks' gestation the patient underwent a fetal pneumonectomy. During the operation the fetal lung mass was successfully resected, however the fetus experienced marked reduction in myocardial contractility and bradycardia that was unresponsive to resuscitative efforts.

In 2010, Abitayeh and colleagues [2] reported two more cases. The first patient, a 40-year-old primigravida pregnant through artificial insemination, had normal ultrasounds until 22-weeks when a large right-sided, hyperechoic lung mass was noted along with marked mediastinal shift, polyhydramnios, and hydrops. The lesion was thought most consistent with type III CCAM. Because of persistent hydrops, investigators placed a thoracoamniotic shunt. The patient delivered a nonviable infant 2 weeks later. Postmortem examination showed a massively enlarged right lung (100 g) and mainstem bronchial atresia. It was specifically mentioned that the atresia was not amenable to “catherization.” The second patient, noted to have a large right-sided lung mass with fetal hydrops at 22 weeks, underwent termination of pregnancy. Postmortem examination confirmed mainstem bronchial atresia, with the right lung weighing 40.6 g.

3. Discussion

MBA is a rare, and to date, lethal lesion that must be distinguished from other right-sided lung masses to permit accurate prenatal counseling and management. Most commonly, fetal lung masses involve a single lobe of the lung and represent a spectrum of developmental disorders related to the variable timing of airway obstruction, including congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration, bronchogenic cyst, congenital lobar emphysema, and bronchial atresia. In our experience, the most common lung malformations show a pattern of segmental bronchial atresia [3,4]. The natural history of these malformations is different depending on their size and rate of growth. It is common that the lesions are largest in the interval between 20 and 26 weeks' gestation, likely owing to a combination of growth of the mass and increased fetal lung fluid production, but later in gestation the increase in size of most lesions slows relative to the growth of the fetus, and some lesion types may become smaller and less obvious on imaging. Rarely, rapidly growing lung masses cause fetal complications owing to compression of surrounding thoracic structures by the mass. Indeed, compression on the fetal esophagus leads to polyhydramnios, compression on the diaphragm and cisterna chyli may lead to lymphovenous obstruction and ascites, and compression of the inferior vena cava and heart may lead to hydrops, heart failure and ultimately fetal demise. Fetal lung masses may be stratified for the risk of developing hydrops and heart failure by the CCAM-volume ratio. Those with CVR > 1.6 are much more likely to develop complications and the need for fetal therapy [3,5,6].

The three cases described here add to the four described previously and extend our understanding of the prenatal features, natural history, and possible treatment options for MBA. This uncommon malformation appears to affect the right lung predominantly, as all 7 reported cases have been right-sided. It is unclear whether there may be a male gender predilection; all 3 of our cases were male, but the gender in the previous cases was not reported. No genetic testing has been reported in patients with MBA. In contrast to the other more common malformations, the prenatal natural history of MBA is severe; fetal hydrops develops by 25 weeks' gestation in nearly all cases, and the risk of maternal mirror syndrome is high. Ultrasound demonstrates characteristic features of this condition, such as a large, echogenic right lung mass with marked mediastinal deviation, diaphragm eversion, and findings of hydrops. Fetal MRI is very useful in the accurate detection of this rare condition, as the diagnosis requires the absence of compressed but otherwise normal right lung tissue, which can be difficult to detect using ultrasound alone.

Whereas the natural history of most fetal lung masses is favorable with survival rates greater than 93%, the natural history for fetuses with MBA is poor, and to date no survivor has been reported. In MBA, the atresia of the conducting airway is at the mainstem bronchus rather than more distal at the lobar or segmental bronchus level. As a result, the entire lung becomes malformed with marked over-distention and air-space maldevelopment. The large size of the lung mass in these patients is reflected in the CVR values much greater than 1.6. Interestingly, the natural history of fetuses with lobar bronchial obstruction, as occurred in congenital lobar over-inflation (CLO; also called congenital lobar emphysema), is favorable, despite the fact that the masses in these patients can sometimes also be quite large, with CVR values in the 2.0–3.5 range. The single lobe involvement and lack of complete bronchial obstruction in most cases of CLO may explain why the improved outcomes associated with this lesion are more favorable than in MBA. The histologic findings in the lung of patients with MBA show changes similar to those of type II or III CCAM, suggesting that airway atresia is a common pathogenesis for many congenital pulmonary malformation processes.

Given that there is no survivor to date, the optimal management for a fetus with MBA remains uncertain. However, given the reported outcomes, it is likely that fetal surgical resection may provide the best hope for survival. Maternal betamethasone has been administered to most of the patients with this condition. Steroids may have contributed to the lack of hydrops in one patient (Case 2), but that lung mass was also smaller (CVR 2.6) compared to the others, and perhaps may have had less complete bronchial obstruction. Given that there are no clear side effects to the multiple doses typically used, it is reasonable to continue the practice of steroid administration in the hope that it helps. Thoracoamniotic shunts have been used successfully in the treatment of fetuses with tension hydrothorax [7] or macrocystic lung masses [8] with hydrops. The use of a shunt to alleviate the distended, obstructed bronchi in a fetus with MBA theoretically could make sense. If the obstructed bronchi could be decompressed at an early stage of lung growth it is possible that hydrops might be averted and lung development may improve. However, the underlying pathology of MBA, closer to type II or III CCAM rather than the large-macrocystic type 1, leads us to believe that a thoracoamniotic shunt would not provide adequate decompression that may potentially be offered by open removal of the lesion. Theoretically, early removal of the right-sided lung mass may permit compensatory growth of the left lung. Significant compensatory lung growth has been demonstrated in animal models [9–11] and for fetuses that undergo resection of large fetal lung masses [12] (usually only occupying a single lobe of lung). Similarly, significant left lung growth was seen in our patient in the 20 days following right pneumonectomy. It is likely that the survival of our patient after fetal surgery was limited more by the onset of preterm labor and premature birth than an inherent flaw in the treatment strategy. Our patient’s risk of preterm delivery was increased by her multiparous history and urgent reexploration 18 days following successful fetal surgery. Preterm delivery remains an inherent risk of fetal surgery.

One could still argue that a plausible management option of a fetus with mainstem bronchial atresia is early fetal surgical resection. For most fetal lung mass patients, the indication for open fetal surgical resection is hydrops with signs of evolving heart failure [13,14]. For patients with MBA, it may be preferable to intervene slightly earlier in the evolution of hydrops and heart failure, at a time when the
The hemodynamic status of the fetus is more able to tolerate fetal surgical resection. Our fetal surgical case underwent pneumonectomy at 21 weeks' gestation, three weeks earlier than the case in the series by Keswani, a difference that may explain the initial success. The results of this case provide new insight on the feasibility of fetal surgical intervention in MBA and on the physiologic changes that occur following fetal pneumonectomy. With removal of the mass effect created by the massively enlarged lung, the ascites resolved, and the sonographic Doppler indicators of fetal cardiovascular status improved. This case also highlights the importance of optimizing obstetric management following open fetal surgery, since it is imperative to the ultimate success of the intervention. This study carries the inherent limitations of a retrospective review and it is difficult to draw any conclusions based on such a small number of patients in the series. Given that only two attempts have been made at open fetal pneumonectomy for MBA, we can only speculate the potential benefits of this management strategy.

This is the first report demonstrating that fetal surgical pneumonectomy can be technically performed with resolution of hydrops and compensatory contralateral lung growth; however the patient ultimately died as a result of complications of preterm birth. Mainstem bronchial atresia continues to be a lethal anomaly that presents significant surgical and obstetric challenges. However, as advances in prenatal imaging, fetal surgical techniques and obstetric management strategies continue to evolve, we may make strides to improve the prognosis for fetuses diagnosed with this life-threatening condition.

References