Fetal Intrapericardial Teratoma: Natural History and Management Including Successful In Utero Surgery

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Fetal Intrapericardial Teratoma: Natural History and Management Including Successful In Utero Surgery

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Condensation:
Fetal intrapericardial teratoma can be characterized and monitored through fetal echocardiography with successful management in utero including fetal surgical resection with survival to term.
ABSTRACT

Background:

Intrapericardial teratoma is a rare, lethal tumor often detected in fetal life. Tumor mass and pericardial effusion cause cardiac tamponade, which if relieved, could be life-saving. Optimal timing of intervention and methods for effective fetal treatment are unknown.

Objectives:

We describe our single center experience with fetal intrapericardial teratoma including the first report of successful in utero surgical resection with survival to term.

Methods:

We reviewed our database for suspected fetal intrapericardial teratoma. On fetal ultrasound and echocardiography tumor size was estimated by calculation of an ellipse and analyzed in relation to Doppler-derived fetal cardiac output, venous flow patterns, hydrops and outcome.

Results:

Eight fetuses with suspected intrapericardial teratoma were seen between 2009 and 2015. Gestational age at initial presentation ranged from 21-34 (median 26) weeks. Two cases mimicked the appearance of intrapericardial teratoma, but had no serial change in cardiac output over time and were ultimately determined to be other types of tumor. In 6 cases of true intrapericardial teratoma, tumor growth was extremely rapid and was associated with progressive decline in cardiac output (to < 400 cc/kg/min) manifesting in hydrops and death if left untreated. One case was treated successfully at 31 weeks through ex-utero intrapartum delivery with tumor resection while on placental support. Another case underwent open fetal
surgery and resection at 24 weeks, with resumption of gestation until delivery at 37 weeks with excellent outcome.

Conclusions:

Fetal intrapericardial teratoma can be successfully managed utilizing serial surveillance and by treatment in a timely manner prior to the predictable onset of hydrops, determined through increasing tumor size and a declining cardiac output. Surgical resection in utero is possible, with good result.
INTRODUCTION

Teratoma arising from the pericardium is an extremely rare tumor comprised of endodermal, mesodermal and ectodermal germinal cell lines. Treatment is readily achieved through surgical resection with low incidence of recurrence. However, when intrapericardial teratoma is detected in fetal life, mortality is high. Tumor size can be large and associated with pericardial effusion, the combination of which leads to progressive constraint of filling, cardiac tamponade, fetal hydrops and death.

Treatment of fetal intrapericardial teratoma before birth is a challenge. To date, management most often includes observation with temporizing measures of pericardial fluid drainage or delivery, once the fetus reaches a viable gestational age for postnatal surgical resection. Prenatal resection, if possible, would be an ideal means of treatment. Open fetal surgery for resection of lung lesions is feasible with good results, when performed for impending hydrops prior to onset of severe hemodynamic compromise. A previous attempt at removal of a intrapericardial teratoma in a hydropic fetus did not result in survival. Markers characterizing the course and predicting in-utero deterioration would be helpful in guidance and timing of effective treatment strategies.

The aims of this study are to report our experience with fetal intrapericardial teratoma, offer insight into monitoring by fetal echocardiography and report on the application of innovative
treatment strategies to deal with this lethal condition, including successful in-utero surgical resection.

**METHODS**

Database at the Fetal Heart Program and Center for Fetal Diagnosis and Treatment at The Children’s Hospital of Philadelphia was searched. The diagnosis of intrapericardial teratoma was suspected through ultrasound assessment when a large, irregularly shaped mass of heterogeneous echo-texture appeared to arise from outside of the cardiac chambers and from within the pericardial sac lining. Intrapericardial teratoma is defined as a teratoma arising from *within* the pericardial sac, with parietal pericardium covering, to be distinguished from other masses such as mediastinal teratoma, or other lung lesions, which may share similar physiological consequences but by nature may have a different course and prognosis. Obstetrical ultrasound, fetal echocardiography and clinical course were reviewed for each case as well as pathology data.

All patients underwent detailed obstetrical ultrasound and fetal echocardiography. Notation was made of presence of fluid in body cavities. Fetal hydrops was defined as significant fluid accumulation in 2 or more locations, and in at least one additional space besides the pericardium such as ascites, scalp edema, abdominal wall edema, or skin edema. Tumor location was characterized and dimensions measured. As tumor shape was irregular but mostly round or oval, estimate of size was obtained by measuring orthogonal maximum length and
maximum width and calculating the area of an ellipse \[\text{area (cm}^2) = 3.14 \times \frac{1}{2} \times \text{maximum long axis diameter} \times \frac{1}{2} \times \text{maximum short axis diameter}\].

Doppler echocardiography was performed and tracings were obtained in the ductus venosus (DV) and umbilical vein (UV) as measures reflecting impediment to forward venous flow. Abnormal DV flow pattern was defined as near absent or reversed flow with atrial contraction; abnormal UV flow pattern was defined as presence of venous pulsations. Cardiac output was estimated for right and left ventricle by pulsed-wave Doppler interrogation across the pulmonic and aortic valves respectively, using the formula: \[\text{flow} = \frac{3.14 \times \text{semilunar valve radius}^2 \times \text{velocity-time integral} \times \text{heart rate}}{\text{estimated weight in kilograms}}\]. Normal combined right and left cardiac output in the fetus is 400-500 cc/kg/min.

Quantitative data are described as range (median) values. Pearson correlation coefficient was used to assess relationship of tumor size to cardiac output.

**RESULTS**

Between 2009 and 2015, eight cases of suspected fetal intrapericardial teratoma were identified (Table 1). Gestational age at initial presentation ranged from 21-34 (median 26) weeks. Serial fetal evaluations with two or more assessments were made in 5 patients; only 1 evaluation was performed in each of 3 patients (cases 2, 7, 8) presenting with severe hydrops.
All cases had moderate to large circumferential pericardial effusion at initial presentation. In seven cases, tumor mass appeared to compress the right atrium and impair filling of the right ventricle. In one (case 5) the tumor appeared to arise from the pericardium adjacent to the left atrium, extending leftward and cephalad into the upper mediastinum. Pathology diagnosis confirmed mature teratoma with multiple germinal cell lines in 6 of 8 patients. The mass in cases 5 & 6 mimicked the fetal echocardiographic appearance of intrapericardial teratoma by exhibiting characteristics of irregular shape, and heterogeneous echotexture, however on postnatal pathology were determined to be an ascending aortic teratoma and an intracardiac atrial hemangioma, respectively.

**Clinical course, management strategies and outcomes.**

Case 1 presented at 22 weeks gestation in a 27 year old woman with morbid obesity, hypertension and gestational diabetes. A rapidly progressive increase in tumor size was noted, with a large cystic component. At 26 weeks gestation, fetal pericardiocentesis was performed and 4 cc of serous fluid removed. Tumor growth continued unabated, with onset of hydrops at 28 weeks and fetal demise at 30 weeks (figure 1).

Case 2 presented in a 31 year old woman at 31 weeks gestation with a large tumor, ascites and hydrops. Judgment favored delivery as opposed to continued fetal management. Due to concerns about circulatory instability during transition from fetal to postnatal life, an EXIT (ex-utero intrapartum therapy) delivery was undertaken. The fetal head and chest were partially delivered through a uterine hysterotomy. While still maintained on uteroplacental support,
median sternotomy was performed. The tumor was resected by dividing fibrous attachments to the epicardium. To optimize respiratory mechanics, paracentesis was performed and 20 cc of ascites fluid removed prior to cord clamping and fetal ventilation. After 62 days of neonatal intensive care, the patient was discharged and at 4 years of age has no evidence of tumor recurrence.

Case 3 presented in a 35 year old woman at 21 weeks gestation without hydrops, but at 23 weeks a rim of ascites developed, indicating early onset of hydrops. The family did not desire further management and fetal death ensued at 25 weeks.

Case 4 presented in a 21 year old woman at 22 weeks gestation without hydrops. Within 1 week of follow up a rim of ascites developed with increase in tumor size. Realizing the poor prognosis if left to the natural state, multidisciplinary deliberation was undertaken and the family agreed to pursue open fetal surgical resection of the tumor. At 24 weeks gestational age, maternal laparotomy and anterior hysterotomy were performed. Upper extremities were brought through the hysterotomy leaving the head and body inside the uterus, exposing the fetal chest (Figures 2 and supplemental video). A 24 gauge IV was placed in the right hand and a pulse oximeter on the left. Monitoring of cardiac status was achieved through continuous intraoperative fetal echocardiography. Midline incision and sternotomy exposed a bulging pericardium. In order to avoid the negative circulatory consequences of sudden relief of cardiac tamponade, the fetus was pre-loaded with 10 mL/kg of blood. Manipulation of the teratoma led to compromise of cardiac function with onset of severe mitral and tricuspid valve
regurgitation and transient fetal bradycardia, which resolved following cessation of tension. Debulking of the teratoma was undertaken due to tumor size. At completion of removal, echocardiography revealed decreased filling of the heart and another 10 mL/kg of blood infused. Once hemostasis was ensured, a vessel loop was utilized as a drain in the anterior chest and the pericardium was left open. The sternum was closed, the fetus returned to the uterine cavity and maternal hysterotomy closed. Postoperative course was uneventful, and serial weekly maternal-fetal assessments were performed until 37 weeks gestation with delivery through low transverse Caesarean section. At birth, the tricuspid valve annulus was smaller than mitral on echocardiography, reflecting the residual of right-sided compression, without evidence for cyanosis or cardiac symptoms. The child is well at 3 years of age with no evidence of tumor recurrence.

Case 5 presented in a 23 year old woman at 34 weeks gestation. A large irregularly shaped mass was noted in the left chest, compressing the left atrium and left ventricle and encasing the ascending aorta as it extended anteriorly and cephalad. There was a large pericardial effusions and the tumor was quite large, yet there was no hydrops and no change in size of the mass during 3 weeks of follow-up. Elective delivery was undertaken at 37 weeks gestation, and at cardiac surgery a large encapsulated tumor extending into the upper left mediastinum, not adherent to any part of the heart, was noted. The pericardium was opened and a large bloody effusion drained. The tumor was mobilized and found to arise from the ascending aorta, above the sino-tubular junction, extended onto the underside of the arch and was adherent to the aortic wall. During dissection, the aorta was entered and cardiopulmonary bypass (CPB)
initiated. After resection, homograft patch reconstruction of the aorta was performed. The patient could not be separated from CPB and after a period of support with extracorporeal membrane oxygenation, expired.

Case 6 presented in a 31 year old woman at 33 weeks gestation. An irregularly shaped tumor associated with a large pericardial effusion was noted in the right atrioventricular groove with appearance of compression of the right atrium. Serial evaluation over 4 weeks revealed minimal increase in tumor size and no signs of hydrops. Delivery was elected at 37 weeks and the infant was stable at birth. Surgery was performed in the first week of life and the tumor was noted to be inside the right atrium, adherent to and pushing out the right atrial free wall. Excision was undertaken using CPB and pathology revealed hemangioma.

Cases 7 and 8 presented at 26 weeks gestation. At time of initial presentation, tumors were very large and hydrops present. No intervention was undertaken due to the severe condition of the fetus and fetal demise subsequently occurred at 27 and 28 weeks gestation.

**Tumor size, echocardiographic markers and progression of findings.**

Tumor size at initial fetal evaluation ranged from 2.5 to 19.6 (median 7.0) cm$^2$. In the five cases of serial evaluation, tumor size increased to a maximum of 3.6-24.7 (median 6.4) cm$^2$. Rapid tumor growth occurred in 3 cases of confirmed intrapericardial teratoma (cases 1, 3 & 4), with minimal growth in 2 cases, ultimately determined on pathology not to be of pericardial origin (cases 5 & 6).
No hydrops was present with tumor size < 5 cm²; florid hydrops was present when tumor size was > 9 cm² in the cases of confirmed intrapericardial teratoma. In cases 3 and 4, a small rim of ascites reflecting early onset of hydrops was present with tumor size 6.4 and 5.8 cm², respectively. Tumor size in case 5 (not of pericardial origin and positioned leftward) grew to be 24.6 cm², however there were no signs of hydrops.

Abnormal DV/UV flow patterns were seen in all cases of hydrops. In the two cases of a small rim of ascites, one did (case 3) and one did not (case 4) exhibit DV/UV flow abnormalities.

Combined cardiac output at initial presentation ranged from 253-510 (median 393) cc/kg/min. In all six cases of pathology confirmed intrapericardial teratoma, cardiac output initially presented at, or rapidly declined to, an abnormal level below 400 cc/kg/min (figure 3). In the two cases of tumor not of pericardial origin (cases 5 & 6) cardiac output remained in the normal range above 400 cc/kg/min during follow-up (figure 4). Analysis of the six confirmed intrapericardial teratoma cases at all evaluated points in time demonstrates combined cardiac output to be inversely related to tumor size (Pearson rho = - 0.66, p<0.001).

COMMENT

Management of intrapericardial teratoma presenting before birth is a challenge. Prenatal diagnosis often culminates in fetal death. Resection of an intrapericardial teratoma after birth is
curative, however treating the fetus with this condition in-utero has to date been difficult. In the current era of improved prenatal imaging and cardiovascular surveillance utilizing fetal echocardiography and the potential for in utero treatment through techniques of fetal surgery, survival with good outcome may be possible. In this series, we describe parameters that characterize fetal intrapericardial teratoma and report on successful treatment through surgical resection in a 31 week fetus delivered through EXIT strategy and in a 24 week fetus cured through open fetal surgery.

A number of observations specifically characterize intrapericardial teratoma and help distinguish it from other similar appearing tumors. In our cases of pathology confirmed intrapericardial teratoma, tumor growth was extremely rapid, occurring over a period of a few weeks. Increasing tumor mass led to cardiac tamponade, with physiological consequences of diminished cardiac output, fetal hydrops and death if left untreated. Decreasing cardiac output was directly related to increasing tumor size. Furthermore, in all cases of true intrapericardial teratoma the mass arose on the right side from the region of the pericardial reflection at the junction of the ascending aorta and right atrial appendage, was well encapsulated, and did not invade adjacent structures. In the two cases mimicking intrapericardial teratoma there was no significant change in tumor size over time and no evidence for an abnormally low cardiac output. In addition, both presented late in gestation, resulting in stable newborn infants, delivered at nearly full term. Despite the presence of a giant size tumor in case 5, Doppler flow patterns in the DV/UV were normal and there was no hydrops. Location of the tumor on the left side may explain the absence of these findings, as the right side of the heart was
unaffected, with preservation of right ventricle filling. Combined cardiac output remained normal despite a large mass, perhaps through compensatory mechanisms of flow preservation through the right side of the heart and the ductus arteriosus. Such mechanisms of compensation are not possible when the right side of the heart is compressed as in true intrapericardial teratoma. Aggressive rapid tumor growth, with progressive cardiac tamponade, is thus the distinctive hallmarks of this condition.

Early detection of a relatively small tumor that is suspicious for intrapericardial teratoma based on appearance and location demands careful and frequent surveillance for change in tumor size and serial assessment of cardiac output. The objectives are to catch the condition prior to the onset of hydrops, so as to avoid treatment while in an unstable, potentially injured state. Abnormalities of Doppler flow patterns in the DV/UV were mostly present only once onset of hydrops had occurred, therefore this parameter may not be an appropriate predictor of forthcoming un-wellness, but rather reflect cardiovascular instability already present. An increase in tumor size and an abnormally low or declining cardiac output are therefore indications for treatment. Although a cystic component may contribute to the overall tumor mass in intrapericardial teratoma, drainage of the cyst may not adequately relieve tamponade and does not inhibit rapid tumor growth, as seen in our first case. Similarly pericardiocentesis alone may not lead to sufficient relief of tamponade, if the bulk of the tumor mass is left untouched. The most effective treatment is tumor resection.
How best to approach the problem based on gestational age? Outcomes for the premature infant beyond 28 weeks gestation are good. When faced with progressive increase in tumor size and decline in cardiac output, delivery after 28 weeks utilizing the EXIT strategy approach is reasonable. If access cannot be achieved with delivery and postnatal resection due to young gestational age, then successful fetal surgery is possible if undertaken prior to the onset of fetal hydrops. We describe the first successful case of fetal surgery for resection of intrapericardial teratoma, performed at 24 weeks gestation. A major contributor to our success was the ability to perform the fetal surgery prior to the onset of hydrops and thus avoid the development of a critically ill fetus. Although cardiac output at the time of fetal surgery was low (310 cc/kg/min), there was only a small rim of ascites and no abnormality of ductus venosus or umbilical vein flow, indicating a window of opportunity to intervene. Serial follow-up of combined cardiac output revealed an increase to normal levels after fetal surgery.

Fetal intrapericardial teratoma can be successfully treated utilizing serial surveillance and employing treatment prior to the onset of hydrops. Tumor size, location and measured combined cardiac output aids in decision-making. Prompt referral for treatment to a multidisciplinary fetal therapy center at the time of first diagnosis or at the earliest signs of increase in tumor size or decline in cardiac output is essential. If referred within the appropriate window of opportunity, consideration for fetal surgery and resection are possible, with good result.
Acknowledgments:

We wish to acknowledge the superb work of our obstetrical ultrasound and fetal echocardiography staff in obtaining the high quality images used in this study. Dr. Rychik’s effort and this work are possible through the support of the Robert and Dolores Harrington endowed chair in pediatric cardiology at The Children’s Hospital of Philadelphia.
REFERENCES:


FIGURE LEGEND:

Figure 1. A. Intrapericardial teratoma following fetal demise (case 1). The tumor has grown to over three times the size of the heart. Note the rightward location of the mass. DA, descending aorta; H, heart; IVC, inferior vena cava; PT, pericardial teratoma.

B. Tumor is transected and displays the heterogeneity in tissue make-up and texture typical for a teratoma.

Figure 2. Fetal surgery median sternotomy (case 4). A. The fetal arms (large open arrows) and chest are brought through the maternal hysterotomy (yellow arrows) for exposure.

B. The intrapericardial teratoma (arrow) is gently pulled away from the heart and resected (see supplemental video of the fetal surgery and tumor resection).

Figure 3. Graph displaying estimate of tumor size (black squares) and combined cardiac output (red circles) versus gestational age at all points of evaluation for the 6 fetuses with confirmed intrapericardial teratoma. Note the increase in tumor size (dotted line) and decrease in combined cardiac output (solid red line) with increasing gestational age. CCO, combined cardiac output.

Figure 4. Graph displaying estimate of tumor size (black squares) and combined cardiac output (red circles) versus gestational age at all points of evaluation for the fetus with atrial hemangioma (case 5) and the fetus with aortic teratoma (case 6). Although quite large at initial
presentation in case 6, no significant growth in tumor size was noted during the period of prenatal surveillance. Combined cardiac output remained normal at above 400 ml/kg/min without any decrease throughout the period of prenatal surveillance for either of these cases, both ultimately identified as not being intrapericardial teratoma.
Table 1

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<th>Hydrops</th>
<th>GA (wks)</th>
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CCO, combined cardiac output; DV, ductus venosus; EXIT, ex utero intrapartum delivery; GA, gestational age; UV, umbilical vein; wks, weeks.