Congenital cervical teratoma in association with neuronal migration disorder

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Financial support information
Dr. Saito-Benz received PhD stipend from the Otago Masonic Charitable Trust when this article was written.

Case report
Ms A, a primiparous 30-year-old woman with an IVF pregnancy was referred to our regional maternal-fetal medicine (MFM) service following an abnormal morphology scan at 20 weeks gestation. Two-dimensional ultrasound scan at 23 weeks gestation revealed a right-sided neck mass, clenched hands, agenesis of the corpus callosum (ACC), absent Cavum Septum Pellucidum and colpocephaly (Figure 1). The neck mass measured 35x18x23mm, was largely cystic with a solid central component, and there was an associated superior displacement of the right mandible. The ultrasound appearance raised a strong suspicion of a congenital cervical teratoma. An amniotic fluid sample was taken at 23 weeks gestation and analyzed by array Comparative Genomic Hybridization (aCGH) using the Agilent ISCA (v2) 60K oligonucleotide array platform. The result was a normal female hybridization pattern with no abnormality detected. Maternal cell contamination was excluded by multiplex QF-PCR (quantitative fluorescent) analysis.

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A multidisciplinary team comprising of quaternary maternal-fetal medicine, neonatology, ENT, pediatric surgery, pediatric radiology and clinical genetics were consulted to determine the optimal antenatal and perinatal management.

Fetal MRI (Phillips Achieva 1.5T) was performed at 25 weeks gestation, to assess the degree of airway compromise and anatomy of the tumor in relation to surrounding tissues (Figure 2a). It revealed compression and displacement of the oropharynx and hypopharynx by a predominantly cystic lesion extending from the right parapharyngeal region. Diffuse cortical abnormality of the frontal lobes and grey matter heterotopia was suspected in addition to the known ACC. In view of the additional intracranial findings and persistently clenched hands, parents were counseled of the high risk of a long-term and severe neurological impairment. However, as there was no similar case in the literature to guide accurate prognostication, the parents opted to continue with pregnancy.

The mass progressively enlarged to 79x64x53mm by 34 weeks gestation, with associated polyhydramnios from 31 weeks. There was no significant vascularity within the mass nor development of hydrops fetalis. Due to the development of polyhydramnios there was concern about adequacy and safety of the postnatal airway. Thoracic volumes consistently appeared to be adequate with no evidence of pulmonary hypoplasia. The possibility of the Ex-utero Intrapartum Treatment (EXIT) procedure was discussed with the parents. Following extensive multidisciplinary team discussion a decision was made to aspirate the cystic component to assess reversibility of the airway obstruction. At 35 weeks gestation, 140ml of straw-coloured fluid was aspirated under ultrasound guidance from the presumed cervical teratoma. Amniodrainage of 1000ml was additionally performed. Post-aspiration fetal MRI demonstrated successful decompression of the cystic component of the mass and complete resolution of the airway obstruction. Fetal ultrasound scan 2 days later showed some re-accumulation of fluid within the cystic component of the mass although it remained significantly smaller compared to pre-drainage.

Cytology of the cystic aspirate showed abundant macrophages and epithelioid cells. It was also noted to contain beta-2 transferrin, a sensitive and specific marker of cerebrospinal fluid (CSF) (1). However, the immunohistochemistry did not assist with diagnosis of cervical teratoma.

Ms A developed spontaneous late preterm labor at 36 weeks and 2 days gestation. Bedside ultrasound scan showed significant re-accumulation of fluid within the cyst, similar to the pre-drainage volume. A further 130ml of fluid was therefore successfully aspirated from the cyst immediately prior to delivery to optimize neonatal airway management. A paired theatre set-up was coordinated whereby the lower segment caesarean section was performed in one theatre and the baby was then immediately transferred to the adjacent ENT theatre for airway management. The delivery was attended by the maternal-fetal medicine specialist, pediatric anesthetist, pediatric ENT surgeon and neonatologist. Baby A was born in good condition; however, despite adequate respiratory effort, due to concerns about airway adequacy was electively intubated at birth with an uncuffed oral 3.5 mm endotracheal tube.

Baby A was transferred to Neonatal Intensive Care Unit (NICU), and was stable on minimal ventilation settings with no supplementary oxygen requirement. The decompressed cyst re-accumulated quickly with a visible change in size within the first few hours of life.

Postnatal examination revealed short palpebral fissures with micro-ophthalmia, a large neck mass that supero-posteriorly displaced the right ear and mild finger contractures on all digits, but no other dysmorphic features.

Baby A was noted to be hypotonic with reduced spontaneous movement but with regular breathing effort, stable heart rate and blood pressure. She was unable to suckle feed, in part due to the presence of the neck mass, but tolerated full milk feeds via naso-gastric tube.
There was no clinical seizure activity, but conventional and amplitude-integrated electroencephalograms (EEG) were performed to assess the background cortical activity. Both were significantly abnormal with discontinuous activity patterns suggestive of a significant abnormality of brain maturation.

Postnatal CT and MRI of the brain and neck on day 2 of life allowed more detailed anatomical assessment of the mass and intracranial abnormality. The large complex solid-cystic mass within the right neck contained fat and calcium (Figure 2b). There was involvement of the right middle and inner ear and significant effacement of the pharynx (Figure 2c). The mass was intimately associated with the right internal jugular vein and internal carotid arteries at the skull base. The mass was felt to be most in keeping with the presumed diagnosis of a teratoma. The intracranial abnormality seen on the postnatal MRI was more extensive than antenatal imaging had suggested, and confirmed extensive diffuse polymicrogyria throughout the cortex, grey matter heterotopia, ACC and dysmorphic lateral ventricles.

The intimacy of the tumor with major blood vessels and extension into the temporal bone limited surgical options; complete resection was extremely unlikely to be achievable, with a high risk of peri-operative mortality due to tumor placement and degree of invasion. Additionally, the extensive neuronal migration disorder alone posed a bleak prognosis with a high likelihood of severe neurodevelopmental disability and major seizure disorder. The MDT team, following an extensive discussion with parents over a course of two weeks, came to a conclusion that palliative comfort care rather than extensive surgical intervention would be in baby A’s best interest.

Baby A was extubated successfully on day 8 and remained well saturated in room air without respiratory support or supplemental oxygen. The patency of her airway post-extubation was maintained by needle aspiration of the cyst, under sucrose analgesia, every 2-3 days, whenever the fluid reaccumulation caused tense swelling of the cyst with resultant airway compromise and stridor.

Baby A was therefore discharged home on day 18 of life with support from the community palliative care team, neonatal nursing team and a consultant neonatal medicine.
Etiology
The most accepted theory on the pathogenesis of congenital teratoma is that of abnormal proliferation of pluripotent cells sequestered during early embryonic development. A number of genetic abnormalities have been reported in association with congenital or childhood teratomas, including aneuploidies, marker chromosomes, ring chromosomes, and copy number variants (3, 7, 8, 10). Sacrococcygeal teratomas are well described in Currarino syndrome (MIM:176450) caused by pathogenic variants in MNX1, however there are no well described single gene causes of congenital cervical teratomas (7-9).

Prenatal diagnosis
Congenital cervical teratomas are rare but an important differential diagnosis to consider in a fetus or a neonate presenting with a neck mass. The commonest cause of fetal cervicofacial tumors is lymphatic malformation (75%) followed by teratoma/epignathus (21%), haemangioma (2%) and thyroid tumor (2%) (10).

With advances in technology it is now possible to identify congenital cervical teratomas by 2D ultrasound scan as early as 15-17 weeks gestation (3). Cervical teratomas may be cystic or solid but frequently contain calcification, which helps differentiate them from other causes of a fetal neck mass. Absence of calcification, however, does not exclude the diagnosis of teratoma (11,12). Classically cervical teratomas are found anteriorly and close to the midline. In contrast, lymphangioma, haemangioma and branchial cysts are typically found more posteriorly and laterally. Based on the location, echogenicity and vascularity of lesions, ultrasound examination is usually sufficient to reliably diagnose congenital cervical teratomas (10).

Beta-2-transferrin is a product of neuraminidase activity and is found in CSF and perilymph. While it has high sensitivity and specificity for CSF and is useful in identifying a breach of intracranial space (1), it has a limited value in congenital cervical teratomas because of the relatively common finding of mature CSF-secreting tissue within the tumor itself (40-100%) (13).

Accurate early diagnosis of congenital cervical teratoma enables clinicians to inform parents of the potential prognosis and optimize prenatal and perinatal management. Once the diagnosis is suspected, close monitoring is mandatory to enable early identification of clinically significant airway narrowing and/or polyhydramnios. Antenatal 3D ultrasound and fetal MRI are strongly recommended for further assessment of the tumor extent, airway patency, and associated abnormalities (5, 6, 14, 15).

Association with intracranial abnormalities
In the absence of an underlying genetic abnormality, congenital cervical teratomas are usually isolated phenomena (16). While intracranial extensions of cervical teratomas have been described, true associations of intracranial pathology with extracranial teratomas are extremely rare (Table 1). The pathophysiological mechanism underpinning these associations is currently not understood.
To the Authors' best knowledge, this is the first report of a congenital cervical teratoma with ACC and extensive neuronal migration disorder.

**Prenatal and perinatal intervention**

In all cases, early prenatal involvement of a multidisciplinary team, including maternal-fetal medicine, geneticists, neonatologists, and pediatric ENT surgeons, is strongly recommended. De Backer et al. (19) and Hirose et al. (20) have proposed treatment algorithms for prenatally diagnosed cervical teratomas. It is generally recommended that prenatally identified airway obstruction should be managed by Ex-utero Intrapartum Treatment (EXIT) at or close to term with the facility to perform Operation On Placental Support (OOPS). If polyhydramnios poses a risk of preterm labor amniodrainage should be performed.

In the presence of significant fetal compromise, Hirose et al. (20) recommend fetal intervention below 28 weeks gestation and delivery thereafter. In-utero surgical resection of the cervical teratoma has successfully been performed at around 24 weeks gestation (13, 20). However, fetal surgery poses a significant risk of intraoperative mortality, and such intervention should be reserved as a 'life-saving' measure when the risk of fetal demise from cardiovascular compromise and/or hydrops fetalis outweighs the risk of fetal intervention.

We propose that in-utero aspiration of cervical teratomas can be a beneficial adjunct to the conventional amniodrainage(EXIT) procedure approach when the teratoma contains a large cystic component. In-utero aspiration has a number of advantages. First, management of fetal airway obstruction by tumor resection is likely to promote normal lung development and avoid potentially life-threatening pulmonary hypoplasia. Second, oral intubation during the EXIT procedure is more likely to be successful if the tumor is reduced in size prior to delivery, avoiding the need for a more invasive surgical airway.

In the current case, repeated in-utero aspiration clearly demonstrated the reversibility of the airway obstruction and obviated the need for an EXIT procedure.

While the EXIT procedure has been shown to benefit infants with prenatal airway compromise, it is not without risks to the mothers (21-23). The EXIT procedure requires mothers to receive general anesthesia and agents to promote uterine relaxation in order to maintain placental support for the fetus. Consequently, significant intrapartum blood loss may require management in the forms of volume replacement, blood transfusion and use of inotropic support. Additionally, Noah et al. found an increased risk of postoperative wound infection following the EXIT procedure compared with conventional caesarean section (24). Determining the optimal timing of the EXIT procedure is challenging as the risk of preterm labor in a center without necessary expertise should be weighed against the socio-economic and financial costs of relocating family to a quaternary center (25).

More recently, novel therapeutic techniques such as fetal endoscopic tracheal intubation (26) and fetal airway reconstruction (14) have been proposed as potential future treatment options in management of fetal neck mass but are not yet part of routine clinical practice.

**Prognosis and follow-up**

Overall, congenital teratomas have the highest risks of fetal and neonatal deaths among prenatally diagnosed fetal tumors (27). For congenital cervical teratomas, the degree of airway obstruction is the single most significant prognostic factor (19). If an adequate airway cannot be secured shortly after birth, neonatal hypoxia, anoxic brain injury and death ensue rapidly. Additionally, cervical teratomas, compared with similarly sized neck tumors of other origin, are more likely to cause pulmonary hypoplasia in the fetus due to their relatively solid, incompressible nature (14). Currently, the reported mortality rate for congenital cervical teratomas with airway obstruction is 30-50% (19, 28, 29). However, it is plausible that with increasing accessibility to more advanced perinatal airway management, this figure may improve.

For isolated congenital cervical teratomas, prognosis beyond the immediate perinatal period is determined by whether or not the tumor can be completely re-

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Table 1. Previously reported head and neck teratomas with associated intracranial abnormality.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Year of publication</th>
<th>Location of teratoma</th>
<th>Intracranial abnormality</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipp et al. (17)</td>
<td>1995</td>
<td>Palatal</td>
<td>Dandy-Walker malformation</td>
<td>Fetal demise</td>
</tr>
<tr>
<td>Goldstein et al. (18)</td>
<td>2005</td>
<td>Cervical</td>
<td>Agenesis of corpus callosum and subarachnoid cyst</td>
<td>Termination of pregnancy</td>
</tr>
<tr>
<td>Zielinski et al. (10)</td>
<td>2015</td>
<td>Cervical</td>
<td>Cerebellar and rhombencephalon anomalies</td>
<td>Fetal demise</td>
</tr>
<tr>
<td>Present study</td>
<td>-</td>
<td>Cervical</td>
<td>Agenesis of corpus callosum and neuronal migration disorder</td>
<td>Postnatal demise on day 20</td>
</tr>
</tbody>
</table>
A multidisciplinary team is crucial to enable individualized care and achieving optimal short and long-term outcomes. In a review of 31 cases of head and neck teratomas with intracranial extension, only 4 children survived without complications following a complete resection of tumor. Long-term complications are contingent on the degree of disruption to normal tissue that results from surgical resection of the tumor; complications include recurrence of disease and possible malignant transformation, cranial nerve dysfunctions, facial disfigurement and thyroid dysfunction. Poor prognostic factors include intracranial extension of the teratoma, presence of other anomalies and underlying genetic abnormalities (5, 30). Clinical, radiological (MRI or CT) and biochemical (AFP) follow-up are recommended to monitor for recurrence of tumor (6) and management of any post-operative complications. Multidisciplinary approach is therefore crucial in optimizing functional and neurocognitive outcomes of infants with congenital cervical teratomas.

Conclusion

There is a paucity of literature available to assist parental decision-making when an antenatal diagnosis of cervical teratoma with cortical abnormality is made. To date, no post-natal outcomes have been described, limiting the ability of parents and their medical teams to make informed decisions about termination of pregnancy versus postnatal intervention and/or palliative care. In selected cases such as this, careful maternal, fetal and postnatal management may enable short-duration but high-quality survival in the neonatal period.

Although the mainstay perinatal management of cervical teratomas complicated by airway obstruction is the EXIT procedure with or without OOPT, we report successful in-utero decompression of cervical teratoma with resolution of the airway obstruction obviating the need for the EXIT procedure. As this approach also enables lung maturation, preventing the development of pulmonary hypoplasia, it should be considered when the tumor is largely cystic.

In all cases early diagnosis and involvement of a wider multidisciplinary team is crucial to enable individualized care and achieving optimal short and long-term outcomes for these infants and their family. Decisions about the risks and benefits to the family of pregnancy continuance are challenging and highly emotive. Adequately informing these discussions with medical literature that explores the full range of potential outcomes is an essential part of antenatal counseling for these high-risk babies and their families.

Acknowledgements

The Authors would like to thank parents and staff of the Wellington Neonatal Intensive Care Unit.

Disclosure of interest

The Authors report no conflict of interest.

References