Congenital mesoblastic nephroma with distant metastasis in a premature twin gestation

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ABSTRACT
Congenital mesoblastic nephroma (CMN) is a rare renal tumor of infancy. Here, we present a case of CMN presenting in a 29 week premature male in a twin gestation. An abdominal mass had been noted on prenatal ultrasound. It was initially treated with right radical nephrectomy. Pathology was consistent with cellular type CMN. Three months postoperatively, the patient developed pulmonary metastasis and underwent wedge resection of the right lung lesion. He subsequently underwent adjuvant chemotherapy, to which he has responded well. We discuss the presentation and management of patients with CMN and address the indications for postoperative chemotherapy.

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1. Introduction
Congenital mesoblastic nephroma (CMN) is a rare renal tumor, accounting for up to 4% of all pediatric renal tumors; however, it is the most common renal neoplasm in infants up to three months of age [1]. Diagnosis is frequently made in utero as a mass or polyhydramnios identified on prenatal ultrasound. It is generally considered a benign tumor however there are reports of recurrent and metastatic disease [2–6]. Here we present a case of a premature infant from a twin gestation that was diagnosed with CMN and later developed distant metastatic disease.

2. Case report
A 31 year-old G2P1 female, 19 weeks gestation with twin males following in vitro fertilization, presented with premature rupture of membranes for Twin B. This was managed with bed rest therapy. At 27 weeks gestational age, prenatal ultrasound demonstrated an abdominal mass in Twin A. Two weeks later, the mother developed preterm labor, leading to an emergent Caesarean section. Twin A was born at 1360 g with normal amniotic fluid. Twin B was born at 1000 g with oligohydramnios and expired several hours after delivery due to fulminant cardiopulmonary collapse secondary to pulmonary hypoplasia.

Twin A was admitted to the neonatal intensive care unit. The infant was noted to have a large palpable abdominal mass on physical exam. An abdominal ultrasound demonstrated a mass in the right upper quadrant with punctate calcifications; a computed tomography (CT) scan showed a 8 × 5.6 × 6.9 cm mass with no evidence of a right kidney or adrenal gland, and the small calcifications from the ultrasound were not seen (Fig. 1). Following medical stabilization in the neonatal intensive care unit he was taken to the operating room on day of life 12.

Exploratory laparotomy was performed via a transverse abdominal incision. A 7.5 × 5.5 × 5 cm mass was noted from the right kidney (Fig. 2). Upon inspection of the abdomen there was no evidence of metastatic disease. A right radical nephrectomy was performed with no evidence of any gross residual tumor. The postoperative course was complicated by respiratory insufficiency and required mechanical ventilation for three weeks following surgery.

Pathology results were consistent with CMN, cellular subtype. The tumor was noted to infiltrate the adjacent renal parenchyma with positive medial, peri-hilar margins, making this a Stage III tumor. Fluorescent in situ hybridization (FISH) did not identify ETV6-NTRK3 gene rearrangement or any karyotype anomalies. Given the patient’s prematurity and size, the decision was made to defer adjuvant chemotherapy and a program of close surveillance.

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Fourteen weeks after tumor resection (post-conceptual age 45 weeks), a right upper lobe lung nodule was noted on surveillance chest x-ray. This was further evaluated with CT scan (Fig. 3), which also demonstrated several lesions in the liver. There was no radiographic evidence of local recurrence. One week later, the patient underwent a right thoracotomy and wedge resection of the 2 cm right upper lobe lung nodule (Fig. 4). Pathology was consistent with congenital mesoblastic nephroma, confirming metastatic disease.

Following resection of the lung nodule, and with evidence of possible metastatic disease to the liver, adjuvant chemotherapy was started. After completing a complete course of vincristine, cyclophosphamide and dactomycin, the infant has demonstrated complete response based on repeat imaging of the liver lesions.

3. Discussion

Although exceedingly rare, CMN is the most common renal tumor diagnosed within the first three months of life [6,7]. There is a 2:1 male predominance. The typical findings on presentation are a palpable abdominal mass, hematuria, hypertension and polyhydramnios [8–10]. Prenatal diagnosis can be made with ultrasound as in the present case [8,11]. Postnatal diagnosis can be made with renal ultrasound and CT scan.

There are three types of histologic subtypes of CMN: classic (24–58%), cellular (42–66%), and mixed-type (10%), with the cellular and mixed-type known to have more aggressive characteristics [6,7]. CMN is characterized by its spindle cells but the cellular type is distinguished by larger nuclei, hypercellularity, increased mitotic activity and the presence of necrosis [12]. The cellular type is associated with a t(12;15)(p12;q25) translocation resulting in a ETV6-NTRK3 fusion gene. This finding supports that CMN is more closely related to infantile (congenital) fibrosarcoma (IF) rather than nephroblastoma (Wilms tumor) [13]; in fact some authors refer to CMN as “infantile renal fibrosarcoma” in order to tie the two processes together [14].

CMN was first distinguished as a separate entity from nephroblastoma by Bolande et al. in 1967 [7]. Radical nephrectomy alone was considered adequate management. With the discovery of the ‘atypical’ or cellular variant by Joshi et al. the possibility of recurrent and metastatic disease became apparent [2,3]. The risk for recurrent or metastatic disease is associated with intraoperative tumor spillage, positive surgical margins, cellular type histology and open biopsy [6,15]. Reports of metastatic disease are rare, however known sites of distant metastasis include lung, liver, heart, and brain [2,3,5,15–21].
There is debate over the role of neoadjuvant and adjuvant chemotherapy and radiation in the treatment of CMN. Early attempts at treating CMN with chemotherapy regimens used in nephroblastoma have not been successful [4,16]. Given the discovery of the ETV6-NTRK3 fusion gene and close relation of CMN to IF, advancements have been made in the use of ‘sarcoma’ based chemotherapy regimens in patients with CMN with high risk for or presence of recurrent or metastatic disease. Remission has been seen with the use of regimens consisting of doxorubicin, vincristine, and actinomycin/cyclophosphamide [4,5].

The identification of patients at high risk for recurrent or metastatic disease remains a challenge. Overall survival with CMN has been cited at 95%, however recurrent disease has been associated with a mortality as high as 50% [4]. In the largest case series to date from the Gesellschaft für Pädiatrische Onkologie und Hämatologie it was demonstrated that surgical resection alone was sufficient management in the majority of patients. The high risk subset for recurrence and metastases included patients with stage III disease who had the cellular subtype. In their series of 50 patients with CMN, five patients had cellular subtype stage III disease; two patients did not receive adjuvant chemotherapy and had recurrence, while three patients did receive adjuvant chemotherapy and did not have recurrent disease [5].

This case is of interest for several reasons. First, it is the only known published case of an infant born from twin gestation with CMN. Second, at 29 weeks this patient is one of the youngest infants who was diagnosed with CMN, particularly with the cellular subtype, which is more common in older infants. Further, the decision to not give adjuvant chemotherapy following resection in this type of scenario is controversial. It is impossible to say whether the patient would have avoided metastases had he received adjuvant chemotherapy. Similarly, it is unknown what residual side effects may have resulted from chemotherapy administration in such a young infant. On the other hand, his good response to chemotherapy thus far may in fact validate the initial avoidance of adjuvant chemotherapy until it is needed in the setting of confirmed recurrent or metastatic disease. This would in turn stress the importance of a thorough surveillance program to identify recurrent or metastatic disease at the earliest time point.

In conclusion, we report a case of a premature infant from a twin gestation with stage III CMN who went on to develop distant metastases. This case highlights the dilemma involved in deciding whether to administer adjuvant chemotherapy to young infants at higher risk for recurrence or metastases. At the present time such decisions must be made on a case-by-case basis, as the rarity of this condition precludes any type of prospective comparative analysis. Reports such as this on individual cases or case series may in time lead to the development of consensus-based guidelines in order to guide future treatment.

References