Ultrasound Obstet. Gynecol. 10 (1997) 68–73

Clinical and perinatal sonographic features of congenital adrenal cystic neuroblastoma: a case report with review of the literature

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Key words: ADRENAL GLAND, HEMORRHAGE, NEUROBLASTOMA, CYST, RESOLUTION

ABSTRACT

Cystic formation in association with adrenal neuroblastoma may be related to hemorrhage and necrosis of the tumor. We present an unusual case of congenital cystic fetal neuroblastoma of the right adrenal gland detected at 37 weeks' gestation which evolved into a complex echogenic mass 6 weeks after birth. Surgical exploration revealed a 3.5 × 3 × 3 cm right complex adrenal tumor which was resected. The infant did well 10 weeks after tumor resection. Typically adrenal hemorrhage may appear sonographically to be entirely echogenic, of mixed echogenicity, or anechoic when first imaged. Gradually, the texture of the hematoma will evolve and become more cystic and echolucent on follow-up ultrasound examinations. In contrast, our case of congenital adrenal cystic neuroblastoma became more complex after resolution of the hemorrhagic cyst. This case suggests that adrenal hemorrhage and adrenal cystic neuroblastoma with a hemorrhagic cyst have different sonographic appearances. We suggest that additional imaging and surgical intervention should be considered whenever a cystic suprarenal mass becomes more complex after resolution and demonstrates no significant decrease in size in postnatal examinations.

INTRODUCTION

Neuroblastoma is a tumor of the postganglionic sympathetic neurons and is the most common extracranial solid tumor found in children[1]. In half of the cases, the tumor arises in the adrenal gland[1]. Neuroblastoma occurs in about 1 per 10 000 to 1 per 30 000 live births[1–3]. Purely cystic lesions have been reported in fetal neuroblastoma, but are rare in infancy[4]. The cystic formation in association with neuroblastoma may be related to hemorrhage and necrosis of a tumor. Purely cystic neuroblastoma may represent neuroblastoma *in situ* and may indicate a favorable postnatal prognosis[4–8]. The incidence of adrenal hemorrhage based on an extensive necropsy series has been estimated at approximately 1.7 per 1000 births[9]. The etiologies of adrenal hemorrhage include birth trauma, perinatal hypoxia, septicemia, shock, thrombocytopenia, congenital syphilis and disseminated intravascular coagulation[9–13]. Most hemorrhages are reported to occur at birth or during the early neonatal period[10]. The differential diagnosis between adrenal cystic neuroblastoma and a purely adrenal hemorrhage is difficult, because the blood flow on ultrasound examination may be absent in both cases[14] and the urine vanillylmandelic acid levels have been reported to be normal in fetal or neonatal cystic neuroblastoma[4,14,15].

We present our observation of an anechoic simple cyst in the fetal adrenal gland which evolved to a complex echogenic mass by 6 weeks postnatally and prompted surgery for resection of an adrenal neuroblastoma. The postnatal evolution on ultrasonography manifested an unusual natural history of fetal adrenal cystic neuroblastoma. We review the literature for other cases of congenital adrenal cystic neuroblastoma detected by perinatal sonography.

CASE REPORT

A 23-year-old woman, gravida 3 para 2, was referred for sonographic evaluation at 37 weeks' gestation because of a fetal intra-abdominal mass. The mother had two healthy children. She had none of the following conditions during the course of her pregnancy: maternal exposure to hydantoin, phenobarbital, alcohol, teratogenic agents or

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Received 15–10–96
Revised 8–1–97
Accepted 18–1–97

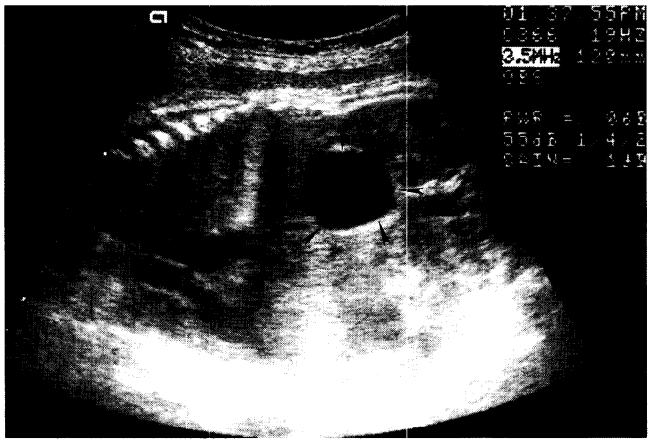

Figure 1 Fetal sonogram at 37 weeks' gestation, showing an anechoic simple cyst (arrowheads) superior to the right kidney

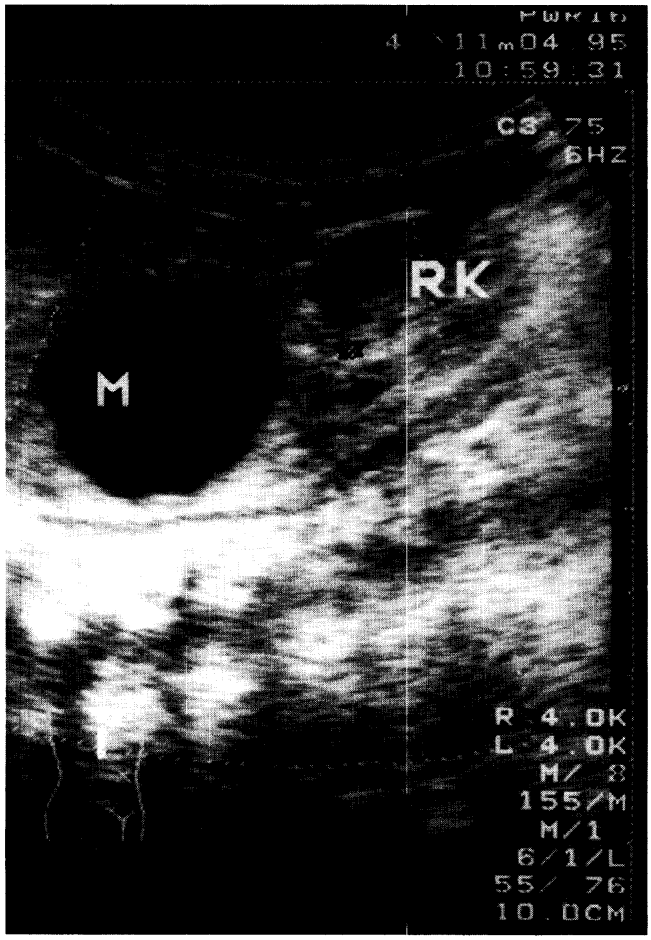

Figure 2 Neonatal sonogram at age 3 days, demonstrating a suprarenal cystic mass (M) and the right kidney (RK)

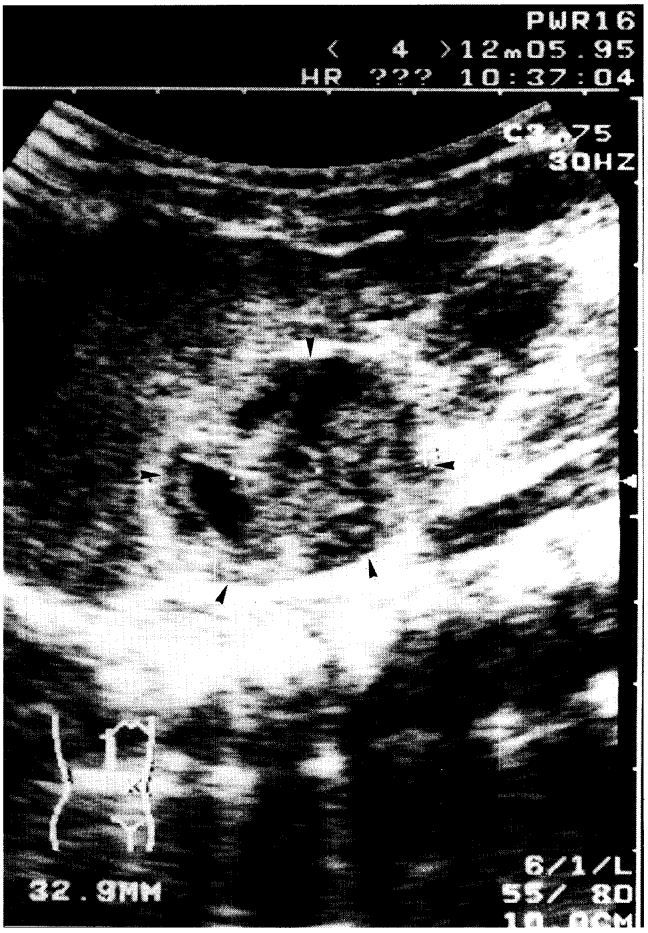

Figure 3 At age 6 weeks, the neuroblastoma appears with mixed echogenicity (arrowheads) on ultrasound scanning

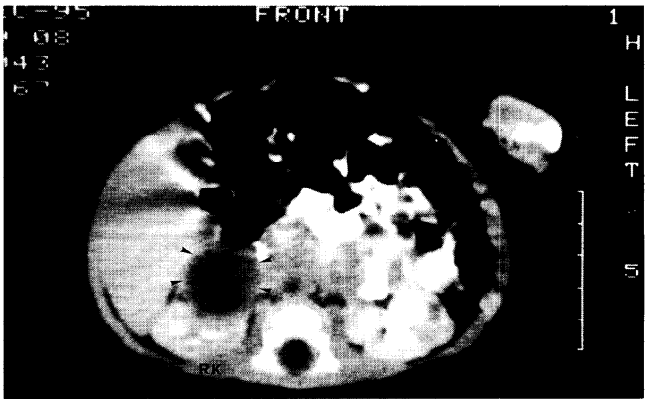

Figure 4 Neonatal CT scan with contrast enhancement at age 6 weeks, demonstrating a well-defined hypodense nodular lesion (arrowheads) over the upper pole of the right kidney

radiation, familial neuroblastoma, maternal diabetes and infectious diseases. The father's age was 34 years. The Chinese couple involved in this pregnancy were unrelated and there was no family history of malformations. Ultrasound examination of the 37-week fetus demonstrated a 3×3 cm anechoic simple cyst (Figure 1) superior to the right kidney without the finding of blood flow by color Doppler and flow imaging. Both kidneys were normal. At 39 weeks' gestation, a 3118-g healthy female baby was delivered vaginally. Labor and delivery proceeded without complication. At birth, no abdominal mass was palpable on physical examination.

Repeat sonography demonstrated an anechoic cystic mass (Figure 2) measuring $3.8 \times 2.6 \times 3.0$ cm over the upper pole of the right kidney. Examination of large blood vessels within the renal pelvis showed no evidence of

Table 1 Clinical features of congenital adrenal cystic neuroblastoma

Reference	*Sonographic diagnosis* (gestational weeks)	*Obstetric complication*	*Prenatal/postnatal sonographic findings*	*Age at resection*	*Postnatal outcome*
Janetschek *et al.*, 1984[2]	34	—	4-cm cystic right adrenal mass at 34 weeks; 6-cm cystic and solid mass at 36 weeks; solid and lagoon-shaped cystic mass a few hours after birth	1 day	stage I, right adrenalectomy, cystic neuroblastoma with central hemorrhagic necrosis, normal urinary catecholamines, no disease at 6 months
Newton *et al.*, 1985[19]	35	pre-eclampsia	4-cm right renal cystic mass at 35 weeks; 5 × 7 cm cystic right flank mass, ascites, right hydronephrosis (suspected) at 36 weeks		fetal hydrops, neonatal death, bilateral adrenal neuroblastoma, diffuse metastases to liver, lung, brain, pituitary, spinal cord and placenta
Atkinson *et al.*, 1986[4]					
case 1	34	—	complex right renal mass; persistent complex suprarenal mass	not reported	stage I, surgical resection, 3.5 × 3.5 × 2.5 cm cystic mass, neuroblastoma *in situ* with hemorrhagic cyst, no disease at 2 years
case 2	32	—	complex left renal mass, left hydronephrosis (suspected); a multiloculated complex, echogenic mass superior and medial to the left kidney	not reported	stage I, surgical resection, 5 × 4 × 3 cm multiloculated mass with solid and cystic components, hemorrhagic cysts and serous cysts, VMA/HVA (–), bone marrow (–), bone scan (–), no disease at 1 year
Giulian *et al.*, 1986[18]	38	—	3.5-cm mixed cystic and solid right suprarenal mass; right adrenal complex mass	3 days	stage I, surgical resection, hemorrhagic congenital neuroblastoma, no disease at 1 year
Sakata *et al.*, 1986[30]	39	—	3.4 × 4.0 cm intra-abdominal cyst; mixed cystic and solid right adrenal mass	19 days	stage I, 5 × 4.5 × 3 cm cystic mass with blood clot and serosanguineous fluid, surgical resection, VMA/HVA (–), LDH (↑), ferritin (↑), bone marrow (–), bone scan (–), no disease at 9 months
Pley *et al.*, 1989[20]	36	maternal hypertension	4-cm left upper abdomen sonotranslucent cobweb-like mass; left hydronephrosis (suspected)	not reported	stage I, surgical resection, encapsulated adrenal neuroblastoma with hemorrhage and necrosis, VMA/HVA (–), no disease at 1 year
Forman *et al.*, 1990[23]					
case 1	4 days before birth	—	right adrenal cystic mass; no change to cystic mass at 6 weeks	not reported	stage II, surgical resection, cystic primary tumor, no disease at 2.8 years
Hosoda *et al.*, 1992[22]	35	—	3.5 × 3.1 cm mixed cystic left suprarenal mass; 3.2 × 3.4 cm mixed cystic left adrenal mass at 4 days	16 days	stage I, 3.5 × 2 × 2 cm hemorrhagic tumor, surgical resection, VMA/HVA (–), NSE (–), non-amplified N-*myc*, hyperdiploidy, no disease at 16 months
Ho *et al.*, 1993[7]					
case 1	30	toxemia	left suprarenal mass at 30 weeks; size increased at 34 weeks; no change to cystic mass at 4 days	13 days	stage IA, 5 × 4 cm cystic mass, surgical resection, bone marrow (–), bone scan (–), VMA/HVA (–), no disease at 9 years

Continued

Table 1 *Continued*

Reference	*Sonographic diagnosis* (gestational weeks)	*Obstetric complication*	*Prenatal/postnatal sonographic findings*	*Age at resection*	*Postnatal outcome*
case 2	36	—	right suprarenal cystic mass; cystic mass at 2 days	8 days	stage IA, 2-cm cystic mass, surgical resection, bone marrow (–), bone scan (–), VMA/HVA (–), no disease at 6 years
case 3	30	—	left suprarenal cystic mass; cystic mass at 6 days and 3 weeks	3 weeks	stage IV-S, 3 × 2 cm cystic variant, surgical resection, bone marrow (+). bone scan (–), no disease at 4 years
case 4	42	—	right suprarenal cystic mass; cystic mass at 3 weeks	6 weeks	stage IA, cystic variant, surgical resection, bone marrow (–), no disease at 4 years
case 5	41	—	right suprarenal cystic mass; 2 × 3 cm mixed solid and cystic mass at 1 month	4 weeks	stage IA, cystic variant, surgical resection, bone marrow (–), no disease at 3 years
case 7	37	—	right suprarenal mass; 2 × 3 cm cystic mass at 2 weeks	3 weeks	stage IA, cystic variant, surgical resection, bone marrow (–), bone scan (–), non-amplified N-*myc*, hyperdiploidy, no disease at 1 year
case 10	39	—	right hydronephrosis (suspected); 1.5-cm right suprarenal cystic mass at 3 weeks; no change to cystic mass at 4 weeks	5 weeks	stage IA, cystic variant, surgical resection, bone marrow (–), skeletal survey (–), VMA/HVA (–), non-amplified N-*myc*, hyperdiploidy, no disease at 3 months
Jennings *et al.*, 1993[31]					
case 1	30	pre-eclampsia	sonolucent left suprarenal mass; left suprarenal mass	12 days	stage IA, surgical resection, cystic neuroblastoma with focal hemorrhage and calcification, bone marrow (–), bone scan (–), VMA/HVA (–), no disease at 10 years
case 2	38	—	3 × 3 cm right cystic–solid suprarenal mass	3 days	stage I, surgical resection, encapsulated neuroblastoma with cystic areas, negative metastatic evaluation, no disease at 5 years
Dreyfus *et al.*, 1994[21]					
case 1	40	—	1.8 × 1 cm left suprarenal cystic mass; 2.9 × 2.8 cm suprarenal cystic mass at 1 month	7 weeks	stage I, left adrenalectomy, 3 × 2 cm cystic neuroblastoma, NSE (↑), normal urinary catecholamines, MIBG scintigraphy (+), no disease at 8 months
case 2	38	—	2.1 × 2.6 cm left suprarenal septated cystic mass; 3 × 2.5 cm cystic adrenal mass	5 weeks	stage I, left adrenalectomy, 2.5 × 1.5 cm cystic neuroblastoma, NSE (↑), MIBG scintigraphy (+), VMA/HVA (–), no disease at 3 months
This case	37	—	3 × 3 cm right suprarenal simple cyst; 3.8 × 2.6 × 3.0 cm right suprarenal cyst at birth; mixed echogenic cystic mass at 6 weeks	6 weeks	stage I, cystic variant, encapsulated neuroblastoma with central hemorrhage, surgical resection, VMA (–), ferritin (–), bone marrow (–), bone scan (–), non-amplified N-*myc*, hyperdiploidy, no disease at 10 months

VMA, vanillylmandelic acid; HVA, homovanillic acid; NSE, neuron-specific enolase; MIBG, metaiodobenzyl guanidine; LDH, lactate dehydrogenase; (↑), increased; (+), positive; (–), normal

thrombosis. A 24-h urinalysis for vanillylmandelic acid was normal and serum lactate dehydrogenase, ferritin and α-fetoprotein levels were within normal limits.

At the age of 6 weeks, subsequent sonographic examination showed that the adrenal cyst had spontaneously evolved into a complex echogenic mass (Figure 3). A computerized tomography (CT) scan revealed a well-defined hypodense nodular lesion over the upper pole of the right kidney (Figure 4). Surgical exploration at the age of 6 weeks revealed a $3.5 \times 3 \times 3$ cm right complex adrenal tumor and the primary tumor was resected. On microscopic examination, the tumor tissues of the neuroblastoma were surrounded by a thick fibrous capsule and central hemorrhage. The tumor was considered a stage I neuroblastoma. It showed hyperdiploid cellular DNA content and absence of amplification of the N-*myc* oncogene. The mixed echogenic mass contained bloody fibrous exudate. The tumor tissues demonstrated the typical appearance of darkly staining clusters of neuroblasts. A radionuclear bone scan, bone marrow aspiration and serial liver sonography were all normal. No further therapy was given. The infant did well 10 months after tumor resection. Peripheral blood karyotyping revealed a normal 46,XX complement.

DISCUSSION

The purely adrenal hemorrhage may be sonographically entirely echogenic, mixed echogenic or anechoic when first imaged, but the texture of the hematoma will gradually evolve and become more cystic and echolucent on follow-up ultrasound examinations[16–18]. In contrast, our case of concomitant adrenal hemorrhage and cystic neuroblastoma became more complex after resolution. The mass shrinkage in this case at follow-up represented absorption of intracystic fluid rather than an absence of the tumor. Our presentation implies that purely adrenal hemorrhage and neuroblastoma with a concomitant adrenal hemorrhagic cyst have different natures and sonographic appearances.

Twenty cases of congenital cystic neuroblastoma located in the adrenal gland have been reported to date (Table 1). These 20 cases and the present case were all detected in the third trimester of pregnancy. Among these 21 cases of congenital adrenal cystic neuroblastoma, 15 were purely cystic and six were mixed solid and cystic when first imaged, 12 were right-sided, eight were left-sided and one was bilateral. The sonotranslucency of fetal cystic neuroblastoma was prenatally diagnosed as hydronephrosis in four cases[4,7,19,20]. Maternal complications such as pre-eclampsia, toxemia or hypertension occurred in four cases. In most cases, the sonotranslucent areas represented hemorrhage and liquified necrosis. The urinary vanillylmandelic acid and homovanillic acid were negative in all (nine of nine) patients who were evaluated preoperatively. Two of three cases had high levels of neuron-specific enolase[21,22]. Metastatic involvement at the time of the initial postnatal examination was found in the bone marrow of one patient[7]. Clinical staging was favorable. Of the 21 patients, 18 had stage I disease, one had stage II disease[23], one had diffuse metastases and died neonatally[19] and one was categorized as stage IV-S[7]. Twenty patients underwent surgical resection of the primary tumor at ages ranging from 1 day to 7 weeks and all these patients remained free of disease on follow-up, ranging from 3 months to 10 years. Diploid cellular DNA content and amplification of the N-*myc* oncogene have been indicated as carrying a poor prognosis, whereas hyperdiploid cellular DNA content and absence of amplification of the N-*myc* oncogene appear to carry a favorable prognosis[24–26]. Such biological characteristics of neuroblastoma cells were assessed in the case reported by Hosada and co-workers[22], the two cases reported by Ho and colleagues[7] and the present case. All four tumors had favorable features of hyperdiploidy and the absence of amplification of the N-*myc* oncogene.

Another common cause of an adrenal cyst in the newborn is adrenal hemorrhage. The fetal adrenal glands are susceptible to hemorrhage because of their relatively large size and vascularity *in utero*[27]. Adrenal hemorrhage of the newborn affects the right side three to four times more commonly than the left side, possibly because of the propensity of the right adrenal gland for compression between the liver and spine and for change in venous pressure[27,28]. Adrenal hemorrhage is usually followed by necrosis and later resolution and regression of the mass with fibrosis and calcification[27,29]. In the present case, the uneventful labor and delivery made the diagnosis of spontaneous adrenal hemorrhage unlikely. Other possible suprarenal cystic masses or lesions at the upper pole of the kidney – including renal cysts, cystic Wilm's tumor, obstructed upper pole duplication anomalies with ectopic ureteral implantation, hepatic cysts, choledochal cysts, ovarian cysts or enteric cysts – should also be considered prenatally and be confirmed postnatally[21].

Prenatal interventions such as aspiration and biopsy of congenital adrenal cysts remain controversial. We consider that *in utero* interventions for these fetuses, with our current knowledge, are unwarranted, because such procedures may not be adequate for diagnosis of a congenital neoplasm. Furthermore, if follow-up of any infant for whom conservative treatment is proposed cannot be assured, surgical removal of the mass may be prudent. We suggest that additional imaging and surgical intervention should be considered whenever a cystic suprarenal mass becomes more complex after resolution of the cyst and demonstrates no significant decrease in size in postnatal examinations, even with a normal urinary vanillylmandelic acid level.

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