

Unusual Case of Beckwith-Wiedemann Syndrome with Spontaneous Resolution of a Hepatic Mass

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Abstract

Beckwith-Wiedemann Syndrome (BWS) is an overgrowth syndrome with risk for embryonal tumors. Over expression of paternal growth promoters and decreased expression of maternal growth suppressors are believed to underlie these tumors. We report a full term, large for date female with BWS. Initial serum alpha fetoprotein (AFP) was 36,790 ng/ml (1,212 - 49,039 ng/ml) on day of life (DOL) 7, which increased to 119,797 ng/ml (704-29,027 ng/ml) by DOL19, warranting evaluation to rule out hepatoblastoma. Abdominal ultrasound (US) and MRI on DOL 20 showed no mass. Thereafter, serial AFP levels quickly declined: 91,681 ng/ml at 1 month, 24092 ng/ml at 2 months, 1207 ng/ml at 3 months of age but the abdominal US at age 3 months (done as part of surveillance) showed a mass in the right lobe of the liver. A repeat US at 3.5 months showed an increase in the size of the mass despite down trending serum AFP (785 ng/ml), and features of a vascular lesion (Hemangioma). Vigilant follow up with US and AFP was continued given the high risk of tumors. Imaging showed a decrease in size of the hepatic mass starting at 4 months of age and complete resolution by 9 months of age; confirming an involuting hemangioma.

In conclusion, this is an unusual case of an isolated hepatic hemangioma associated with BWS that spontaneously resolved. Hemangiomas should be considered in the differential of hepatic masses especially with discordant AFP levels.

Keywords: Beckwith-Wiedemann Syndrome; Spontaneous Resolution; Hepatic Mass

Abbreviations

BWS: Beckwith-Wiedemann Syndrome; AFP: Alpha Fetoprotein; DOL: Day of Life; US: Ultrasound; pUPD: Paternal Uniparental Disomy

Introduction

Beckwith-Wiedemann Syndrome (BWS) is an overgrowth syndrome characterized by anterior abdominal wall defects, macroglossia, dysmorphic facial features, hemihyperplasia, neonatal hypoglycemia, organomegaly and an increased susceptibility to embryonal tumors. It is considered a clinical spectrum and the affected individuals may present with many or few of the clinical features [1]. Infants with BWS have an increased susceptibility to childhood tumors (~8%), including Wilm's Tumor (52% of all tumors), hepatoblastoma (14%),

neuroblastoma (10%), rhabdomyosarcoma (5%), and adrenocortical carcinoma (3%) [2]. Rarely, hepatic hemangioma/hepatoendothelioma have been reported [3-6].

BWS is an imprinting disorder and has been localized to the growth regulating genes on Chromosome 11p15 [7]. Imprinting is an epigenetic phenomenon that allows certain genes from one parent to be expressed while silencing the expression from the other parent [8]. This imprinting is under the control of discrete DNA elements called imprinting centers [9]. The various mechanisms involved in the BWS are loss of methylation of the maternal imprinting center 2 (IC2), paternal uniparental disomy for chromosome (pUPD) 11p15, and gain of methylation on paternal imprinting center 1 (IC1). Overexpression of paternal growth promoters and decreased expression of maternal growth suppressors are thought to underly these tumors. The highest tumor risk (28%) is seen in patients with hypermethylation of IC1 (normally methylated on the paternal allele). Intermediate risk (16%) is seen with pUPD and low risk (2.6%) is seen in hypomethylation of IC2 (normally methylated on the maternal allele).

We report an infant with BWS presenting with hepatic mass and elevated AFP which eventually resolved by 9 months of age without any intervention.

Case Report

Our patient was a full term, large for gestational age baby girl. Pregnancy was complicated by maternal Grave's disease, fetal macrosomia and fetal macroglossia. She was delivered by C/S and had APGAR score of 8 and 9 at 1 and 5 minutes, respectively. At birth, macroglossia, glabellar hemangioma, anterior lobular crease, posterior helical indentation and enlarged umbilical cord with umbilical cord cyst were noted, leading to the clinical diagnosis of BWS. She presented with early transient hypoglycemia which responded well to Diazoxide therapy, which was successfully weaned after 2 months. Methylation sensitive MLPA of 11p15 showed hypermethylation of IC1 (H19) and hypomethylation of IC2 (LIT1), no deletions or duplications were detected. This pattern of abnormal methylation confirmed the clinical diagnosis of BWS, suggestive of segmental pUPD as the underlying mechanism. Peripheral blood karyotype showed normal female chromosomal component.

Tumor surveillance: Initial serum alpha fetoprotein (AFP) was 36,790 ng/ml (1,212 - 49,039 ng/ml) on day of life (DOL) 7, which rapidly increased to 119,797 ng/ml (704 - 29,027 ng/ml) on DOL19. The clinical and molecular diagnosis (pUPD) of BWS with highly elevated AFP raised concern for an underlying hepatoblastoma. Abdominal ultrasound (US) and MRI were performed on DOL 20 and did not show any mass. Serial AFP levels showed a decline over the next 3 months (91,681 ng/ml at 1 month, 24,092 ng/ml at 2 months, 1,207 ng/ml at 3 months). Abdominal US performed at age 3 months as part of routine surveillance, showed a hypoechoic mass (0.7 x 0.5 x 0.6 cm) in the right lobe of the liver. A repeat US at 3.5 months showed an increase in the size of the mass (1.8 x 0.8 x 1.4 cm) (Figure 1) despite down trending serum AFP (785 ng/ml). The mass was well circumscribed, appeared heterogeneous and contained calcifications and peripheral flow on US; MRI done to further characterize the mass showed prompt progressive enhancement beginning peripherally and filling in centrally, suggesting a vascular lesion like a hemangioma. Surgery and Hematooncology recommended close monitoring with US and serum AFP. Serial US imaging showed a decrease in size of the hepatic mass starting at age 4 months (1.1 x 0.6 x 1.1 cm); to 0.8 x 0.4 x 0.7cm at 6 months (Figure 2) and complete resolution at 9 months of age (Figure 3); confirming an involuting hemangioma. Her most recent abdominal US at 28 months also showed no hepatic mass in conjunction with undetectable serum AFP.

Discussion

Beckwith-Wiedemann Syndrome is an overgrowth syndrome with an increased susceptibility to tumors, both malignant and benign [7]. Hepatoblastoma is the second most common malignant tumor seen in BWS whereas hemangiomas are benign tumors that have been reported in a handful of case reports in the literature [3-6]. Hepatoblastomas usually present early in life, typically in the first 30 months and rarely after 5 years of age (Median age at diagnosis in BWS: 6 months). Early identification is important for successful treatment with



Figure 1: Ultrasound of the hepatic mass at 3.5 months (1.8 x 0.8 x 1.4 cm).



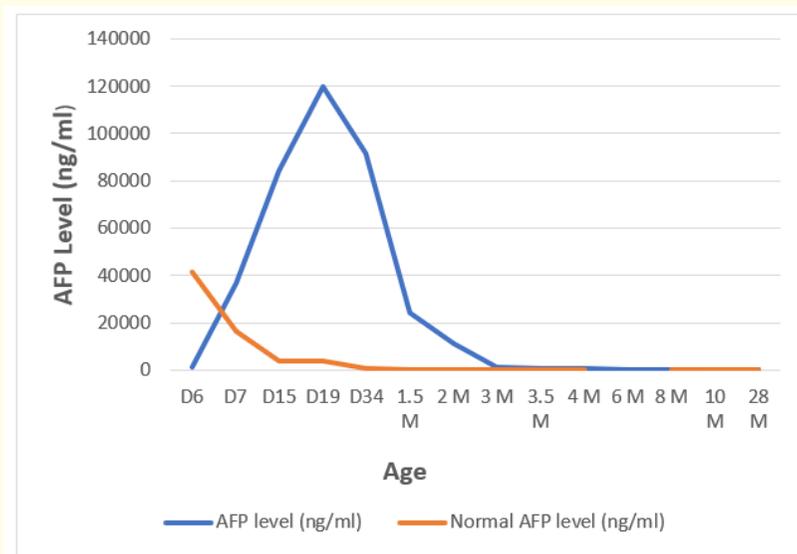
Figure 2: Ultrasound of the hepatic mass at 6 months (0.8 x 0.4 x 0.7cm).



Figure 3: Disappearance of hepatic mass at 9 months.

Age	Serum AFP (ng/ml)	Mean normal AFP (ng/ml)	Size of Mass (on USG, cm)	Morphology of right liver mass (USG)		Doppler flow (USG)	MRI Abdomen
				Abnormal echogenicity (hypoechoic)	Calcifications		
D6	> 1000.0	41687					
D7	36970.7	16107					
D15	84045.7	3631					
D19	119767.4	3631	No mass				No liver mass
D34	91681.7	417					
1.5 M	24092.1	178	No mass				
2 M	10961.4	178					
3 M	1207.5	36	0.7 x 0.5 x 0.6	Yes		No flow	
3.5 M	785.0	36	1.8 x 0.8 x 1.4	Yes	Present	Peripheral	1.6 cm mass likely venous malformation
4 M	458.6	20	1.4 x 1 x 1.3	Yes	Present	Peripheral and central	
5 M			1.1 x 0.6 x 1.1	Yes	Present	Peripheral	
6 M	239.5	13	1.1 x 0.9 x 0.6	Yes	Present		
8 M	61.8	0-6	0.8 x 0.4 x 0.7	Yes	Present		
10 M	35.9	0-6	No mass	Normal echotexture	Absent		
28 M	<6	0-6	No Mass	Normal echotexture	Absent		

Table 1: Table showing the clinical and radiological characteristics of the patient.



Graph 1: AFP trend of our patient.

surgery +/- chemotherapy. Common surveillance practice includes abdominal US every 3 - 4 months till 8 years of age and serial AFP levels every 2 - 3 months for the first 4 years of life for tumor surveillance [10,11]. Screening leads to early identification and better survival rates [11]. Not all experts agree on all components of tumor surveillance, and some suggest omitting AFP monitoring (discussed in detail later). Liver hemangiomas, on the other hand, are benign tumors with a peak incidence in the first 6 months of life [12,13], they can be focal or multifocal, and may or may not involute spontaneously. They are usually asymptomatic and may not require treatment unless they are symptomatic (hemorrhage, transient heart failure, transient coagulopathy and consumptive hypothyroidism) [13].

On ultrasound, hepatoblastomas are seen as well defined, echogenic soft tissue masses, with heterogeneity and variable echogenicity in bigger lesions, with intralesional calcifications [12]. Hemangiomas on the other hand are well defined hyperechoic lesions which may show peripheral feeding vessels on color Doppler and may or may not show calcifications. Because of the overlapping characteristics, differentiating a hemangioma from a hepatoblastoma with ultrasound alone may be difficult [12]. MRI is superior in differentiating the two. Hepatoblastomas appear as hypo-intense masses on T1 images and hyper-intense masses with areas of necrosis and hemorrhage on T2 images [13]. Hemangiomas are also hypo-intense compared to the rest of the liver on T1 images and hyper-intense on T2 image but show peripheral nodular discontinuous enhancement which progresses inward, and they tend to retain contrast on delayed images [13,14].

Newborns with BWS have higher average AFP levels than healthy newborns and show slower rate of decline in infancy [15]. This may present a challenge in interpreting results. In addition, AFP monitoring requires repeated venipunctures at a young age. Considering these difficulties, the 2018 consensus statement on the management of BWS voted against routine monitoring of serum AFP levels for hepatoblastoma surveillance [2,16]. This has not been universally accepted. Some experts recommend serial AFP measurements especially in the genetic forms at a higher risk for developing hepatoblastomas like segmental pUPD and hypermethylation of IC1 [7,17-21] as the increase in AFP usually precedes the appearance of a mass, leading to early detection of hepatoblastoma [22]. A rising trend in the AFP levels is highly suspicious of a hepatoblastoma and may also help in distinguishing a benign hemangioma from a malignant hepatoblastoma [21,23,24].

There have only been a few cases of hemangiomas in BWS reported in the literature. In 1992, Drut, *et al.* reported a 4 months old patient with multiple hepatic hemangiomas, who died soon after diagnosis due to cardiac complications [4]. In 2003, a case was reported in Japan where a 4-month-old baby with BWS was found to have 2 hepatic masses. On biopsy, one mass was a hepatoblastoma (5 x 5 cm) and the other a hemangioma (1.5 x 1.5 cm). Chemotherapy and surgery was needed for the hepatoblastoma (2 courses of chemotherapy with vincristine, cyclophosphamide, Adriamycin, and cisplatin before the surgery and 2 courses after), leading to a decline in the AFP levels. The hemangioma was left in-situ. There was no change in the size of the hemangioma for 2 years [5]. A similar case was reported by Pranvera, *et al.* where a 4-month-old baby presented with 2 hepatic masses (5 cm and 1.5 cm) and an elevated AFP. Four cycles of chemotherapy with cystatin led to regression of the hepatoblastoma along with decline in the AFP level but no change in the size of the other mass. On biopsy, it was found to be a hemangioma [3]. In 2013 Francisco, *et al.* reported a BWS baby with elevated AFP and multiple pulmonary, axillary and hepatic hemangiomas that responded to propranolol and prednisolone [6]. A 4-year-old girl with a splenic mass was reported in 1997 by Herman, *et al.* She underwent partial splenectomy and the mass was found to be a hemangioma on histopathology [25].

In line with the other reported cases, our patient's AFP level continued to decrease despite the presence of a hepatic mass, indicating a benign nature of the lesion. The US and MRI findings suggestive of a hemangioma along with a down trending AFP helped prevent an invasive biopsy in our patient. To the best of our knowledge, this is the only BWS patient in which a hemangioma showed spontaneously involution and ultimately resolved (without any intervention).

Conclusion

Thus, in conclusion, while not commonly reported, our case and the others demonstrate that hemangiomas should be considered in the differential of a mass in BWS. Imaging and Serum AFP levels together can help make the distinction. But since there is a high risk of embryonal tumors, continued surveillance is recommended.

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The authors have no financial relationships relevant to this article to disclose.

Conflicts of Interest

The authors have no conflicts of interest relevant to this article to disclose.

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