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Mesenchymal Hamartoma of the Liver in Beckwith-Wiedemann Syndrome
- A Case Report -

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Beckwith-Wiedemann syndrome is a well-known overgrowth syndrome associated with the presence of a wide variety of anomalies and increased risk of cancers. Less frequently, benign neoplasms also develop. We report a female infant with Beckwith-Wiedemann syndrome who developed a mesenchymal hamartoma of the liver. The patient was born with macroglossia, ear lobe crease, and abdominal distension. Laboratory data showed hypoglycemia, and magnetic resonance image revealed both adrenal enlargement, enhancing mass of the pancreas, and multiple hepatic nodules. The histologic findings of the resected distal pancreas and both adrenals were those of Beckwith-Wiedemann syndrome. Microscopic findings of the liver biopsy specimens were compatible with mesenchymal hamartoma. Hamartoma of the urinary bladder, cardiac fibrous hamartoma, and mixed hamartoma of the liver have been documented previously in association with Beckwith-Wiedemann syndrome. However, to our knowledge, this is the first case report of hepatic mesenchymal hamartoma in Beckwith-Wiedemann syndrome. Because of the paucity of hamartomas in childhood, we should be cautious of other features of Beckwith-Wiedemann syndrome and the present case extends the spectrum of tumor formation in this syndrome.

Key Words : Beckwith-Wiedemann Syndrome -Liver Neoplasms-Hamartoma

Beckwith-Wiedemann syndrome is a congenital overgrowth disorder characterized by exophthalmos, marcoglossia, visceromegaly and neonatal hypoglycemia.[1] Children with BWS have an elevated risk of developing certain malignancies in 4% to 7.5% within the first 7 years.[2] Most of the reported cases are Wilms' tumor, hepatoblastoma, neuroblastoma, adrenocortical carcinoma, pancreatoblastoma and embryonal rhabdomyosarcoma.[1,2] Less frequently, benign tumors including vascular tumor, cardiac hamartoma, chest wall hamartoma, hamartoma of the urinary bladder, adenoma, myxoma, ganglioneuroma, and carcinoid tumor have been reported in cases of Beckwith-Wiedemann syndrome.[2-6] We report a female infant with Beckwith-Wiedemann syndrome harboring a mesenchymal hamartoma of the liver, which was not previously reported in Beckwith-Wiedemann syndrome.

Although mesenchymal hamartoma comprise 17.5% of the benign tumors in patients from birth to 21 years of age,[7,8] the majority of hepatic masses in childhood are metastatic. Primary malignancies are less frequent and benign tumors are relatively rare.[8] In this context, the present case is an extremely rare and unique example of benign tumor in Beckwith-Wiedemann syndrome.

CASE REPORT

The patient was born to a healthy, 26-year-old mother and 29-year-old father with no specific family history. Fetal ultrasonography at 31 weeks of gestation showed abdominal enlargement and polyhydramnios. The patient was born at 31 weeks of gestation, because of preterm premature rupture of membrane. At birth, the birth weight was 2,611 g (+1.5 SD), and the crown-heel length at birth was 47.5 cm (+1.5 SD). The child had tachypnea and respiratory distress (Apgar score 6). Macroglossia, ear lobe crease, and abdominal distension were also observed. Laboratory test showed hypoglycemia (blood glucose: 5 mg/dL). The abdominal magnetic resonance imaging (MRI) disclosed large cystic lesions, not enhanced in post-contrast image, in both adrenal glands, increased vascularity in the tail of pancreas and multiple

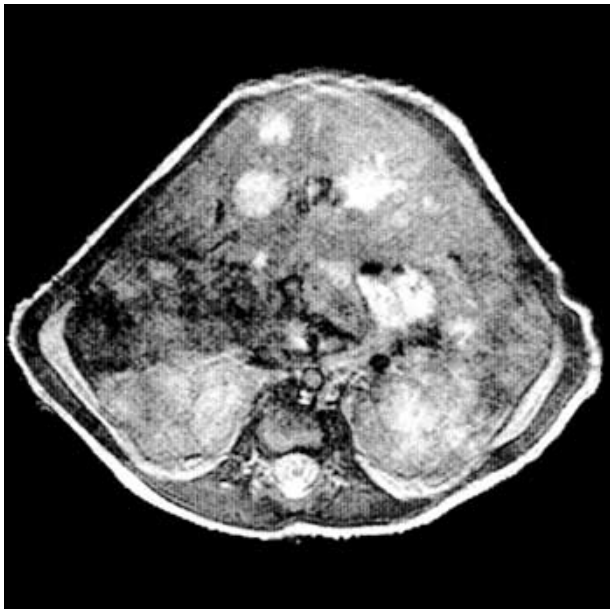

Fig. 1. Abdominal magnetic resonance image reveals multiple enhancing nodules in the liver.

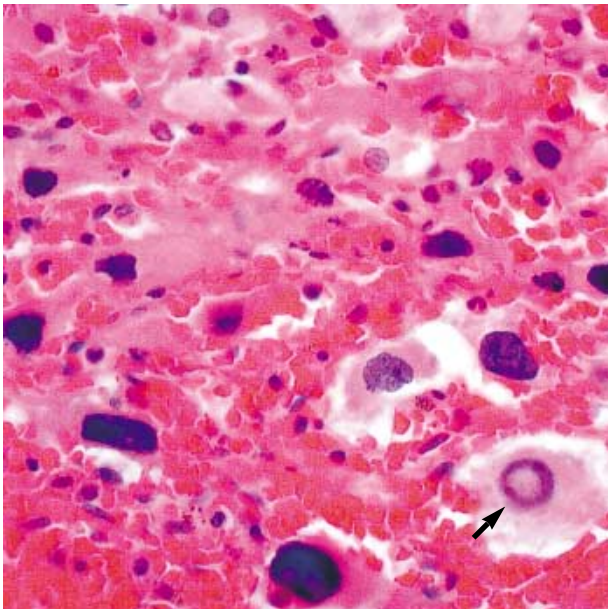

Fig. 3. Microscopic finding of adrenal gland shows cytomegalic cell with pseudoinclusion (arrow).

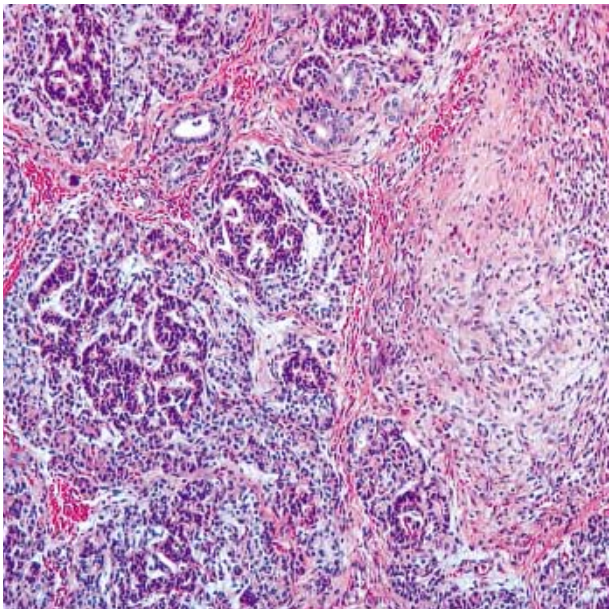

Fig. 2. Microscopic finding of pancreas shows dispersed islet clusters and focal mesenchymal proliferation.

enhancing nodules in the S4, S5 and caudate lobe of the liver (Fig. 1). Under the impression of Beckwith-Wiedemann syndrome, distal pancreatectomy and partial resection of both adrenal glands were performed along with liver biopsy. Gross examination of the resected pancreas, measuring 1.5×1.5 cm, disclosed gray-whitish cut surface, which is confined to pancreas. Microscopically, the pancreas was distorted and largely replaced by glomeruloid cluster of islet tissue with increased size variation and prominent ductuloinsular complex in the lobule. Foci of acinar differentiation were observed in the vicinity of the islets. Abnormally large islet clusters were aggregated and were surrounded by focal areas of mesenchymal proliferation (Fig. 2). Islets were composed of immature cells with plump cytoplasm and large nuclei which were immunoreactive for anti-insulin antibody.

Gross examination of the partially resected left adrenal gland was a piece of yellowish tissue, measuring $0.3 \times 0.4 \times 0.4$ cm. In right adrenal gland, dusky yellow round mass, measuring $1.0 \times 0.8 \times 0.8$ cm, was noted and a fragment of yellow adrenal tissue was attached to one side. The cut surface of right adrenal gland showed cystic lesion filled with chocolate-like materials. Microscopically, both adrenals had prominent fetal zone composed of marked cytomegalic cells. The cytomegalic cells had plump cytoplasm and pleomorphic nuclei with pseudoinclusion (Fig. 3). In the vicinity of fetal zone, focal mesenchymal proliferation was also noted.

Microscopic examination of the liver biopsy specimens disclosed a mesenchymal hamartoma. There was haphazard and variable admixture of mesenchymal, epithelial, and vascular elements. Many tortuous bile ductules, hepatocyte nodules, and arborizing vascular channels were found in the background of loose and edematous mesenchymal component (Fig. 4).

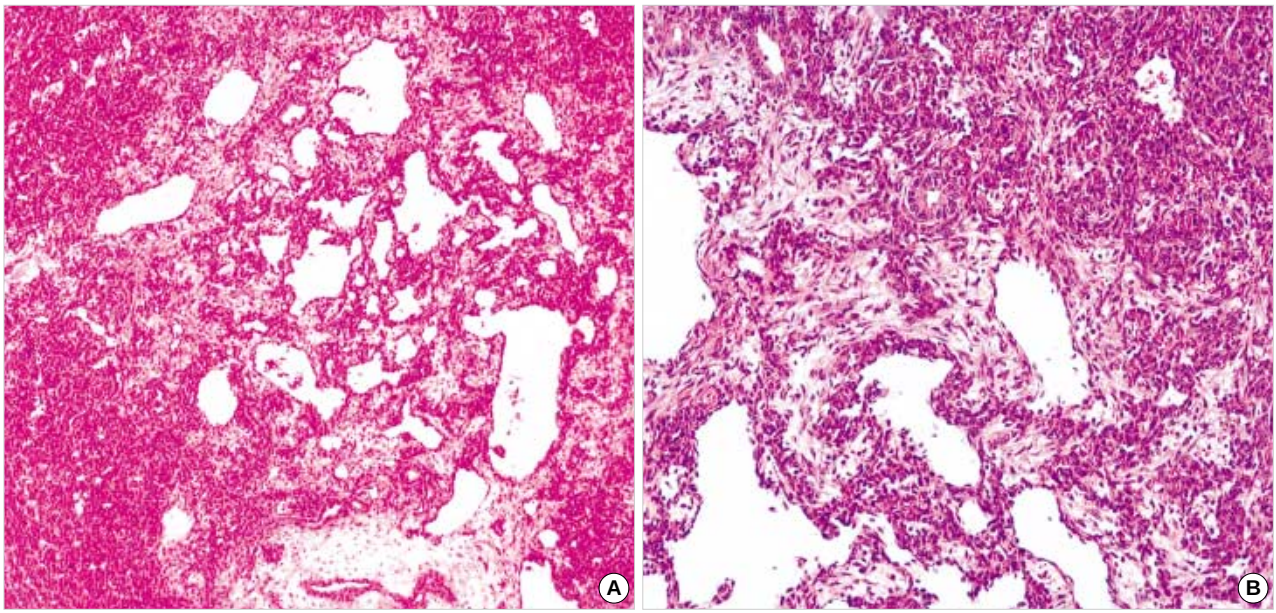

Fig. 4. (A) Low-power view of the liver nodule shows cystic and mesenchymal component. (B) The lesion is composed of the admixture of ducts, arborizing vessels, and irregular liver plate in the background of mesenchymal stroma.

DISCUSSION

Beckwith-Wiedemann syndrome is a relatively common syndrome associated with malformation and elevated risk of developing embryonal tumors. About 85% of Beckwith-Wiedemann syndrome cases are sporadic and the rest appears to be familial.[9,10] In both types, the etiology of Beckwith-Wiedemann syndrome is generally accepted as an effect of genomic imprinting. The linkage studies in familial cases revealed the association with duplication and translocation at the 11p15 position, the locus of *IGF-2, H19, KVLQT* and *P57*^{kip2}.[9] An imbalance of (paternal) growth-promoter activity over (maternal) growth-suppressor activity appears to be main cause of pathophysiology of BWS. The activity of *IGF-2*, essential for normal fetal growth, is regulated by genomic inactivation of the maternal allele.[9] Furthermore, *IGF-2* is frequently overexpressed in BWS-skeletal muscle, adrenal gland, kidney, heart, pancreas, gonads and liver.[11] *IGF-2* has been implicated in the pathogenesis of somatic overgrowth and embryonal tumor of BWS. Among the rest of 11p15.5 gene products, the expression of *H19*, known as candidate for embryonic growth suppression, is maternal allele.[12] On the paternal allele, the *H19* promoter region is heavily methylated at CpG residues, resulting in repression of this gene.[12] In Wilms tumor, biallelic *IGF-2* expression is associated with down-regulation of H19.[13] Children with Beckwith-Wiedemann syndrome frequently have visceromegaly, macroglossia, omphalocele, hemihypertrophy and embryonal tumors such as Wilms' tumor.[14] Taken together, considerable data now suggest that the increased risk of embryonal tumors in BWS are related to the 11p15.5 locus, mainly overexpression of *IGF-2.*

Malignancies have been reported to develop in 7.5-12.5% of children with Beckwith-Wiedemann syndrome,[14] which is much higher than the general population. Benign neoplasms have also been reported in patients with Beckwith-Wiedemann syndrome, although malignancies are more frequent. In the benign tumor of the liver, hamangioendothelioma[3] and mixed hamartoma[15] have been reported. In addition to the mixed hamartoma of liver, one cardiac hamartoma,[4] one hamartoma of urinary bladder,[4] one chest wall hamartoma,[16] and hamartoma of the subcapsular renal cortex[17] were documented. However, to the best of our knowledge, our case is the first mesenchymal hamartoma of the liver in Beckwith-Wiedemann syndrome patients. In the present case, the tumor consisted of a predominance of loose mesenchymal tissue containing multiple small vessels and numerous ductal structures, which explained multiple nodule of the liver on magnetic resonance images.

The recent literature reported the evidence that the type 2 fibroblast growth factor (FGF-2) may be involved in growth of the mesenchymal hamartoma of the liver.[18] The current case is very interesting, in that somatic overgrowth in Beckwith-Wiedemann syndrome has been related to the overexpression of IGF-2,[19] to which the effect of FGF-2 were synergistic.[20] This syner-

gistic effect of growth factor may be an underlying mechanism of the development of congenital hepatic mesenchymal hamartoma in current patient and further study is required.

In conclusion, Beckwith-Wiedemann syndrome has been understood as a somatic overgrowth syndrome involving imprinted growth-regulatory genes. Although benign tumors including hamartomatous lesions are rare in Beckwith-Wiedemann syndrome, the findings in our case suggest that the development of diverse benign tumors are possible in Beckwith-Wiedemann syndrome patients.

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