A case study of Beckwith-Wiedemann Syndrome associated with hepatoblastoma

C. MARTELLI (*) - S. BLANDAMURA (**) - S. MASSARO (***)
M. ZULIAN (****) - G. ALTAVILLA (*****) - M. PIAZZA (******)

Summary: Though the development of neoplasia is frequent with Beckwith-Wiedemann Syndrome its association with hepatoblastoma is extremely rare. Such a case in a fifteen month old child was studied in terms of its clinico-pathological features.

Key words: Beckwith-Wiedemann Syndrome; Hepatoblastoma; Tumor of infancy.

INTRODUCTION

The Beckwith-Wiedemann syndrome (BWS) is a rare anatomo-clinical entity characterized by a large spectrum of congenital anomalies including physical, metabolic and endocrine alterations.

Institute of Pathological Anatomy - Research Laboratory, Ospedale "Al Mare", Venice, Italy (*) (***)
Institute of Pathological Anatomy, University of Padua, Italy (**) (****)

(*) Chief of Pathological Anatomy Research Laboratory, Hospital "Al Mare", Venice, Italy
(**) Assistent professor of Anatomical Pathology, University of Padua, Italy
(***) Assistent, Pathological Anatomy Research Laboratory, Hospital "Al Mare", Venice, Italy
(****) Assistent, Pathological Anatomy Research Laboratory, Hospital "Al Mare", Venice, Italy
(*****) Professor of Pathological Anatomy, University of Padua, Italy
(******) Professor of Pathological Anatomy, University of Padua, Italy

It is frequently associated with the development of an early, often malignant intraabdominal neoplasia.

We present here the more salient clinical and anatomo-pathological features of BWS associated with hepatoblastoma in a fifteen month old child.

CASE HISTORY

A full term male neonate, 4450 gms, was born via vacuum extractor to healthy young parents.

Spontaneous tremor of the limbs, macroglossia, hemihypertrophy of the left half skeleton (most evident in the diameter and length of the left limb), splenomegaly and hepatomegaly were noted at birth.

Furthermore flat angiomatous patches were found on the inferior one third of the limb.

After a few days the tremors disappeared followed by a moderate jaundice, which too regressed after twenty days.

Laboratory data one month later included normal complete blood count, urine analysis and blood chemistry studies except for an increased insulin secretion, 48 mU/ml, from the normal values at the birth as well as a glucose loading curve elevated from an initial value of 30 mg/dl to 78 mg/dl, total serum bilirubin 7.2 mg% (normal 1), direct bilirubin 3.2 mg% (normal to 0.25) and gamma GT 220 mU/ml (normal <60).

Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XX, n. 2, 1993

Table 1.

Determination specimen	Patients	Value	Normal Value
Total bilirubin	122	micromol/L	< 17
Direct bilirubin	54	micromol/L	< 4
GOT	188	U/mol	< 60
GPT	85	U/mol	< 50
Gamma-GT	220	U/mol	< 60
ALP	1150	U/ml	
Alpha-fetoprotein	70	microgms/L	>0.3-0.6<

Cranial cat scan showed a moderate expansion of the left half vault. The patient was released with the diagnosis of Beckwith-Wiedemann Syndrome.

The child was readmitted ten months later with subjaundice and emission of acholic feces. Blood chemistry revealed the following pathologic values (Table 1).

The chromosomal profile studied yielded an euploidic kariotype 46-XY. Chrosomose resolution did not demonstrate anomalies.

BSW associated with pathological liver was reported in the diagnosis.

On readmission the following month, the child's general conditions progressively worsened with a more pronounced hepatomegaly and jaundice. As well, petecchial hemorrhages were noted on the legs.

Three months later neurological disturbances appeared with torpor, areactivity, grave hypotony and areflexia, taking the child to coma and death shortly thereafter. Bronchopneumonia was noted at autopsy.

ANATOMO-PATHOLOGICAL DATA

Somatic asymmetry was noted with the left inferior limb measuring 31 cm and the right 29 cm.

Skeletal musculature was hypotrophic although less evident on the left inferior limb.

On section, the pleural cavity contained a few mls of reddish yellow liquid. The lungs were enlarged and asymmetric; the left weighing 100 gms, the right 125 gms (normal values left 57 gms, right 64 gms).

Lung tissue in the paravertebral zone was dense, red with reddish-grey granular centres. The right lung parenchyma and visceral pleura were disseminated with 1-2 cm bluish-red and yellow haemorrhagic nodules. The tracheal mucosa and larger bronchi were congested. Mucous plugs obstructed the larger bronchi. A few mls of mucous were expelled on squeezing. Mild cardiomegaly 55 gm (normal value 44 gm), modest thickening of wall and a dilatation of the cavities was noted. The epicardium was thin and congested. The myocardium was pale, brownish-pink and fragile. The abdomen was considerably expanded. Minute haemorrhagic petecchie were observed on the fundal and body mucosa of the stomach. The first and second portions of the duodenum were displaced superiorly while the small intestine was shifted to the right. The cecum, ascending and trasverse colon were shifted to the left.

Upon dissection, tracts of moderate to intense congestion were observed.

A marked hepatomegaly 1040 gm (normal value 288 gm) was noted particularly of the right lobe.

It was discovered with sectioning that the right lobe was in part substituted by nodules about 3 cm in diameter. The neoplasm corresponded to 90% of the right lobe and 10% of the left. Sectioned nodules were variegated with areas of haemorrhage and necrosis. The remaining tissue spared from the tumour but damaged by compression and biliary and hematic stasis was about 200 gms. The lumen of the small and medium intrahepatic portal branches contained grey-red thrombi and occasional colliquatives, while the main trunk and larger portal branches were clear. The capsule was thick and nodular in patches.

The spleen (80 gm, normal 26 gms) on section evidenced follicular hypoplasia.

The right kidney was flat and enlongated with respect to the left one.

Both weighed 120 gms, normal value 70 gms.

Posterior thigh and leg muscles appeared brown, edematous, soft and pasty.

ANATOMO-PATHOLOGICAL DIAGNOSIS

These findings indicate epithelial embryonal hepatoblastoma with pleuropulmonari metastasis. Furthermore bilateral broncho-pneumonia, visceromegaly, somatic hemihypertrophy, mesenterium comunis and dolico-sigmoid colon were also evidenced.

The histological tests performed on various organs and stained according to the common procedures showed the following alterations.

The liver neoplasia was composed of a mixed epithelial cell type: polyhedric elements with small nuclei modestly dysmorphic and scant clear cytoplasm in one type. Such elements were arranged in trabeculae defined by sinusoids (Fig. 1). The second less differentiated component had small sized cells, markedly hyperchromatic nuclei and scant cytoplasm. These cells were arranged in clusters, organoid structures, pseudorosettes or acini occasionally with biliary plugs. All neoplastic elements were surrounded by compact fibrous stroma (Fig. 2). Large areas of necrosis and cavitation to neoplastic like coins were also present (Fig. 3). The portal vein and intrahepatic vessels presented lumenal neoplastic thrombosis.

Immunohistochemistry yielded varying amounts of alfa-fetoprotein (normal value: 0.3-0.6 microgms/L). The pancreas showed a marked increase in the number of islets of Langherans (reaching dimensions of 100-200 millimicron) in some areas presenting as the predominant lobular component. A modestly thickened stroma divided the lobes.

Present in the lungs were small metastatic nodes with histologic characteristics analogous to those seen in the primitive hepatic neoplasia.

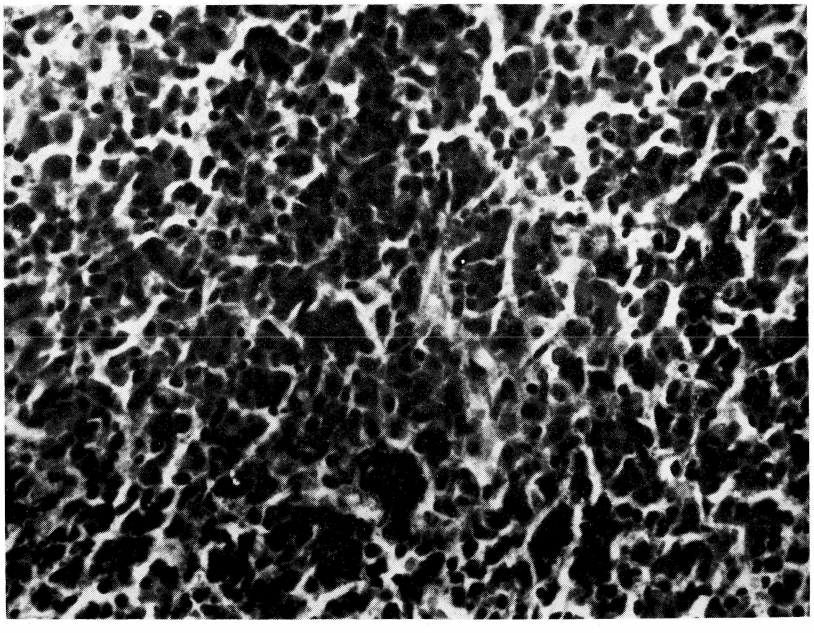

Fig. 1. — Hepatic neoplasia. The neoplastic tissue demostrates dense cellularity. It is composed predominantly of polyedric, epitheliomorphic elements, moderately pleomorphic in size with scarce or discrete amount of cytoplasm. It is generally well-stainable. It forms trabeculae in a radial arrangement. (H. & E. 280 ×).

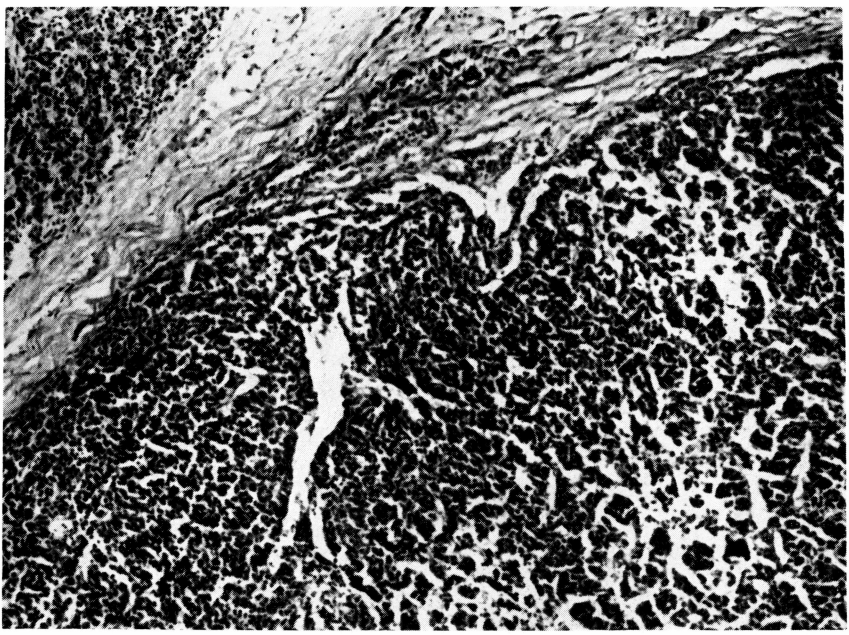

Fig. 2. — Hepatic neoplasia. Fibrous tissue roughly resembling bridges divides fairly uniform neoplastic tissue. This has a faint canalicular and tubular arrangement. (H. & E. 90 ×).

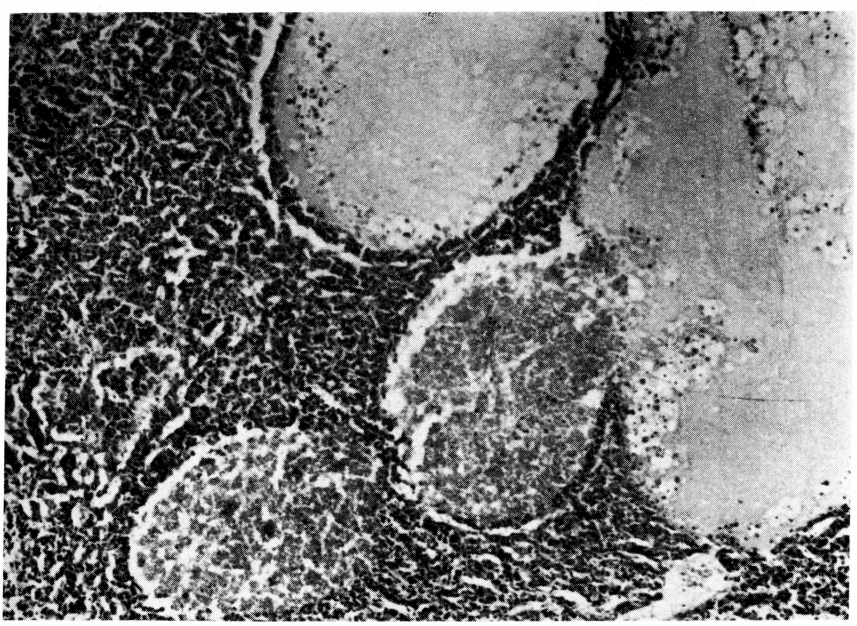

Fig. 3. — Hepatic neoplasia displays hollow formations of varying size tending to confluence. The lumen is filled with mucoid-serous and necrotic material. A lining of gland-like neoplastic elements is seen in some sections. (H. & E. 90 ×).

Degeneration of tubular epithelium was observed in the kidney. Moreover tubules contained irregular calcerous precipitates or bile-like cylinders. There was an increase in number of glomeruli and partial or complete hyalinosis.

A cloudy or vacuolar degeneration was noted in the myocardium.

The gastrocnemius muscular fibers were hypertrophic; some elements presented with granular swelling of the cytoplasm.

Transverse striations were markedly attenuated, disordered or absent. The nuclei in some fascicles were centered, small, shapeless, hypercromatic masses with irregular borders aligned in cords. The connective tissue of the endomysium was moderately and uniformly thickened.

Atrophic-dystrophic myopathy was present in both limbs although more pronounced on the left. This can be explained by compression on the part of nerves and vasculature, by the liver in particular.

Lymph nodes presented with hyperplastic follicles, histiocytosis of the sinuses. The presence of a discrete number of eosinophils and zones of fibrosis were noted in the paraabdominal lymph nodes.

Splenic follicles were enlarged. There was congestion of the pulp cords and conspicuous histiocytosis of the sinuses.

DISCUSSION

The Beckwith Wiedemann syndrome refers to an association of visceromegaly, macroglossia, gigantism and less commonly hemihypertrophy. Beckwith himself considers hemihypertrophy to be simply an incomplete clinical expression of the Beckwith Wiedemann syndrome ([1]).

There has been increased statistical evidence of visceral tumours in patient with BWS and hemihypertrophy ([3, 4]).

Tumours include, Wilms' tumour (60%), adrenal cortical carcinoma (15%), adrenal adenoma, hepatoblastoma and pancreatoblastoma ([1, 2, 8]). Evenmore recently there is documented evidence associating hemihypertrophy, BWS and benign cystic adrenal disease ([7]).

Microscopic examination of fetal adrenal glands in cases with BWS has demonstrated cytomegaly and cortical cysts ([10]).

Recently 2 benign cystic adrenal masses have been reported in relation to the BWS: in 1 a Wilms' tumour has developed ([7]).

Medullary sponge kidney has been associated with hemihypertrophy alone ([9]).

Along with the association of this syndrome with the higher incidence of tumours, recently genetic evidence has been reported for a predisposition for tumourogenesis in the BWS.

Although our chromosomal studies showed a normal 46XY karyotype, anormalities of the short arm of chromosome 11 has been documented with the BWS ([5, 6, 11]).

A proposed common pathogenic mechanism for the development of tumours in the syndrome is the loss of heterogeneity for alleles on this chromosome.

Loss of heterozygosity has also been demonstrated in an adrenal adenoma in a patient with BWS. This loss of heterogeneity may be an early event in tumorigenesis in the BWS ([12, 13]). Therefore these patients with BWS and/or hemihypertrophy should be followed closely to detect these neoplasms and their possible evolutions.

CONCLUSION

In summary this case of Beckwith-Wiedemann syndrome showed many of the classical clinical manifestations reported in literature including somatic hemihypertrophy, mesenterium communis, visceromegaly namely of the liver, lungs, spleen, heart and kidney.

The frequent association of this syndrome with malignant neoplasias is recalled in our cases of BWS with epithelial em-

bryonal hepatoblastoma with pleuropulmonary metastasis.

Although the most primitive tumor in infancy, hepatoblastoma is one of the rarest malignant neoplasias associated with BWS.

Between 1904 to 1988 in Venice, 664 primitive carcinoma of the liver were reported in 55.829 autopsies, 4 were infantile tumors and of these 3 hepatoblastomas.

The one afflicted with BWS was reported in this case study.

REFERENCES

1) Sotelo-Avila C., Gonzales-Crussi F., Fowler J. M.: "Complete and incomplete forms of Beckwith-Wiedemnn syndrome: their oncogenic potential". *J. Pediatr.,* 1980, *96,* 47.
2) Wiedemann H. R.: "Tumor and hemihypertrophy associated with Wiedemann-Beckwith's syndrome". *Eur. J. Pediatr.,* 1983, *141,* 129.
3) Orozco-Florian R., McBride J. A., Favara B. E., Steele A., Brown St. J., Steele P.: "Congenital hepatoblastoma and Beckwith-Wiedemann syndrome: a case study including DNA ploidy profiles of tumor and adrenal cytomegaly". *Pediatr. Pathol.,* 1991, *11,* 131.
4) Emery L. G., Shields M., Shah N., Garbes A.: "Neuroblastoma associated with Beckwith-Wiedemann syndrome". *Cancer,* 1983, *52,* 176.
5) Little M. H., Thomson D. B., Hayward N. K., Smith P. J.: "Loss af alleles on the short arm of chromosome 11 in a hepatoblastoma from a child with Beckwith-Wiedemann syndrome". *Hum Genet,* 1988, *79 (2),* 186.
6) Haas O. A., Zoubek A., Grumayer E. R., Gadner H.: "Constitutional interstitional deletion of 11 pll and pericentric inversion of chromosome 9 in a patient with Wiedemann-Beckwith syndrome and hepatoblastoma". *Cancer Genet. Cytogenet,* 1986, *23,* 95.
7) Walton G. R., Peng B. C. H., Berdon W. E.. Collins M. H., Hensle T. W.: "Cystic adrenal masses in the neonate associated with hemihypertrophy and the relation to the Beckwith-Wiedemann syndrome". *J. Urol.,* 1991, *146,* 580.
8) Drut R., Jones M. C.: "Congenital pancreatoblastoma in a Beckwith-Wiedemann syndrome: an emerging association". *Pespect. Ped. Path.,* 1988, *8,* 331.
9) Harris R. E., Fuchs E. F., Kaempf M. J.: "Medullary sponge kidney and congenital hemihypertrophy: case report and literature review". *J. Urol.,* 1981, *126,* 676.
10) Filippi G., McKusick V. A.: "The Beckwith-Wiedemann syndrome". *Medicine,* 1970, *49,* 279.
11) Waziri M., Patil S. R., Hanson J. W., Bartley J. A.: "Abnormality of chromosome 11 in patients with features of Beckwith-Wiedemann syndrome". *J. Ped.,* 1983, *102,* 873.
12) Koufos A., Hansen M. F., Copeland N. G., Jenkins N. A., Lampkin B. C., Cavenee W. K.: "Loss of heterozygosity in three embryonal tumours suggests a common pathogenetic mechanism". *Nature,* 1985, *316,* 330.
13) Hayward N. K., Little M. H., Mortimer R. H., Clouston W. M., Smith P. J.: "Generation of homogenicity at the c-Ha-ras-1 locus on chromosome 11p in an adrenal adenoma from an adult with Beckwith-Wiedemann syndrome". *Cancer Genet. Cytogenet,* 1988, *30,* 127.

Address reprint requests to:
Prof. M. PIAZZA
Ist. di Anatomia e Istologia Patologica
Università di Padova
Via Gabelli, 61
35121 Padova