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Case Report

Beckwith-Wiedemann syndrome in a child with multifocal Wilms tumor and lateralized overgrowth: A case report ☆

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ABSTRACT

Beckwith-Wiedemann syndrome (BWS) is a rare imprinting disorder and overgrowth syndrome with a prevalence of 1 in 10,000 live births. It is characterized by predilection for embryonal tumor growth, especially Wilms tumor (WT), and manifestations like lateralized overgrowth/hemihypertrophy, macroglossia, macrosomia, anterior abdominal wall defects, and hyperinsulinism.

Our case is a 1 year of female child who presented with abdominal swelling and limb length discrepancies. A clinical diagnosis of BWS was made based on multifocal WT and hepatomegaly and nephromegaly detected on contrast-enhanced abdominal computed tomography and physical examination findings of lateralized overgrowth and umbilical hernia. A molecular genetic test was not available. The patient was started on preoperative chemotherapy with good tolerance.

Clinical criteria can be used to diagnose WBS in a setting where confirmatory molecular testing is unavailable. This will considerably change approaches to management of presenting complications such as WT .

Introduction

Beckwith-Wiedemann syndrome (BWS) is a multisystem overgrowth disease affecting 1 in 10,000 live births and caused by epigenetic or genetic defects at two imprinting centers on chromosome 11p15.5 [1–3]. The molecular abnormalities are frequently mosaic and lead to a range of clinical phenotypes; thus, WBS has recently been renamed spectrum [2,4]. Within this spectrum, patients can be affected by classical

Abbreviations: BWS, Beckwith-Wiedemann syndrome; CT, computed tomography; IC, imprinting center; ILO, isolated lateralized overgrowth; GOM, gain of methylation; LOM, loss of methylation; LO, lateralized overgrowth; NR, nephrogenic rests; pUPD11, paternal uniparental isodisomy of chromosome 11; US, Ultrasound.

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BWS, characterized by findings such as macroglossia, embryonal tumors, and persistent hypoglycemia; isolated lateralized overgrowth; and atypical BWS, in which patients exhibit the genetic abnormality associated with BWS but do not fit the two above clinically [2,4,5]. Clinical features include "cardinal features" that, when present, are more likely to lead to a positive diagnosis and those likely to occur independently in the general pediatric population and have lower diagnostic importance, termed "suggestive features" [2].

A common concern in patients affected by BWS is the predisposition for embryonal tumor development, with an estimated risk of 8%, with the highest risk occurring in the first two years of life [3,5,6]. Wilms tumor (WT) is the most frequently reported tumor, with a 3-5% risk of developing this renal malignancy of embryonal origin [7]. Other tumors include hepatoblastoma, neuroblastoma, rhabdomyosarcoma, and adrenal carcinoma [3,7]. LO indicates a significant increase in the length and/or girth of most or all of one side of the body compared to its contralateral side [8,9]. It can be accompanied by the asymmetric growth of internal organs, and baseline abdominal ultrasound (US) is advised to assess the presence of organomegaly [2,8].

Case history

A 1-year-old female child presented with abdominal swelling and limb length discrepancies. She was born to parents who do not belong to the same family tree. The mother had a regular antenatal follow-up with a complete immunization history, per the Ethiopian national guideline. The antenatal course was uneventful, and no history of maternal medication, harmful drug use, or exposure to radiation during pregnancy was reported. The delivery took place in a hospital with trained medical staff present. The postnatal period was unremarkable, and no pertinent family history was present.

On physical examination, there was a gross limb length and girth discrepancy where the right lower limb was larger and longer than the contralateral side. There were palpable right upper quadrant and right flank region abdominal masses. There was also an umbilical defect with preperitoneal fat herniation that was reducible with gentle finger pressure. The chest was clear on auscultation. The heart sounds were audible with normal S1 and S2. No other dysmorphic features were present. Laboratory tests, including alpha-fetoprotein (AFP), were in the normal range.

Plain radiography of the lower limb shows asymmetry where the right lower limb is larger and longer than the contralateral side (Fig. 1). There were no bony or cartilaginous defects observed.

A contrast-enhanced abdominal CT scan shows 2 separate, well-defined solid masses measuring 8.6 × 5.1 cm and 4.2 × 4.1 cm with heterogeneous contrast enhancement in the lower pole and hilum of the right kidney, respectively. There was associated calyceal dilatation. There was no vascular invasion (Fig. 2).

The right kidney was larger than the left one, and there was also diffuse liver enlargement (Fig. 3). With the clinical impression of BWS and a multifocal right WT, the child was given preoperative chemotherapy, which was well tolerated. However, the parents took the patient home against medical treatment and attempts to find out the patients condition was unsuccessful.

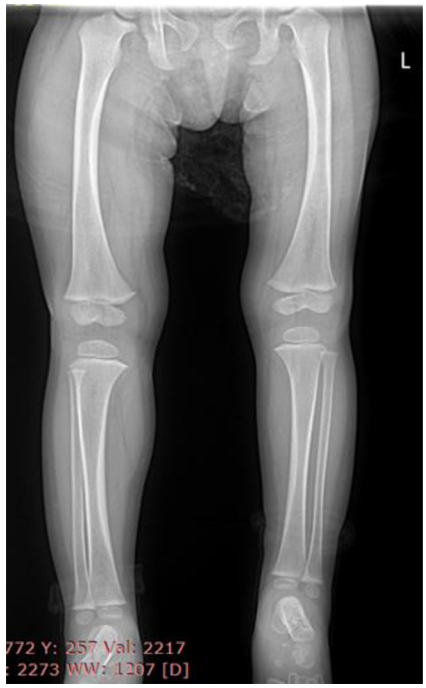

Fig. 1 – Plain lower limb radiography shows a lower limb discrepancy, with the right leg being longer and larger than the left.

Discussion

BWS is the most common overgrowth syndrome and childhood cancer predisposition disorder caused by (epi)genetic changes affecting the BWS critical region on chromosome 11p15 [2,5,10]. The BWS locus is divided into functionally independent telomeric and centromeric domains, each harboring its own imprinting control region and cluster of genes [4,10]. Genes located in the telomeric domain are controlled by IC1, which is methylated on the paternal chromosome, and those located in the centromeric domain by IC2, which is methylated on the maternal chromosome [2]. Overall, a molecular defect affecting imprinted genes can be demonstrated in 80% of patients with BWS. The three most common molecular subtypes of BWS involve methylation abnormalities, including IC2 loss of methylation (50% of patients), IC1 gain of methylation (5-10% of patients), and paternal uniparental isodisomy of chromosome 11 (pUPD11, 20% of patients), which leads to both IC1 GOM and IC2 LOM [5,6,9]. BWS is most commonly caused by numerous postzygotic epimutations that occur sporadically and in a mosaic fashion in affected individuals, resulting in significant phenotypic heterogeneity [11].

Diagnosis of BWS can be made by clinical assessment and/or molecular validation [12]. Molecular subgroups of BWS

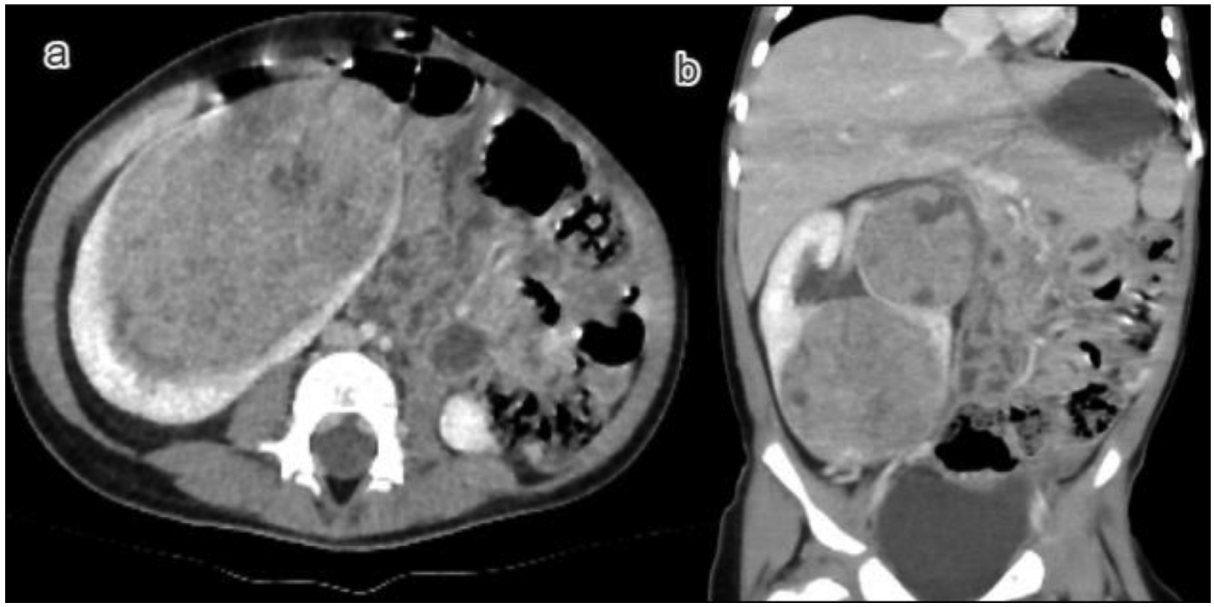

Fig. 2 – An axial (A) and sagittal (B) postcontrast abdominal CT scan shows well defined heterogeneously contrast enhancing intrarenal masses in the right kidney.

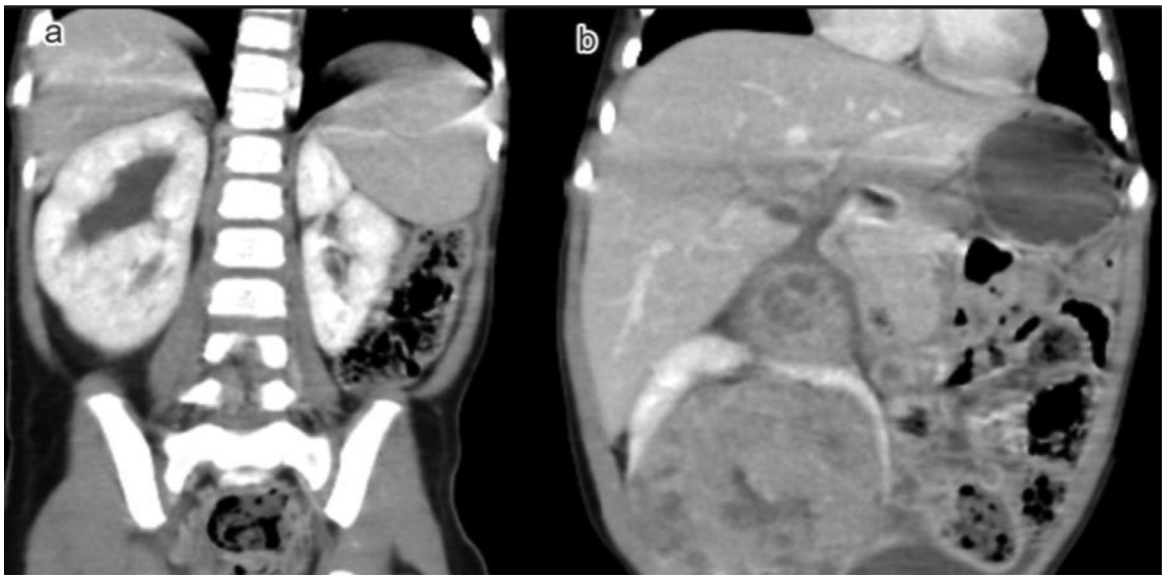

Fig. 3 – Sagittal reformation of a postcontrast CT scan shows an enlarged right kidney (A) and hepatomegaly (B).

are associated with different embryonic tumor risks and have different likelihoods for specific tumors. IC2 LOM, for example, has a lower tumor risk [4,6,10]. Therefore, the precise determination of the molecular subgroup is needed for precise monitoring and treatment [10,12]. A confirmatory genetic test was not pursued in our patient as it was unavailable. From previous epi (genotype) correlation evidence, IC1 GOM and pUPD11 are associated with organomegaly and LO phenotypes and predispose to WT, findings present in our case [5,6]. A higher clinical score may also correlate with a positive molecular genetic test result in patients [9].

Clinical diagnosis of this syndrome is based on the presence of cardial features such as lateralized overgrowth, multifocal and/or bilateral WT, or nephroblastomatosis, and less specific suggestive features include typical BWS tumors, organomegaly, umbilical hernia, and/or diastasis recti, and facial naevus flammeus. Cardinal and supportive features contribute two and one point to the total score, respectively, and at least two points are required to trigger a specific molecular test and four to make a clinical diagnosis even in the absence of molecular confirmation of an 11p15 anomaly [2,4]. However, a positive molecular test allows making a diagnosis in cases with <4 points and supports the clinical diagnosis in those with ≥ 4 points in addition to stratifying tumor risk [1]. Our patient has cardinal features of multifocal WT and LO and suggestive features of hepatomegaly and

nephromegaly, as well as an umbilical hernia, thus having six points that allow a clinical diagnosis of WBS to be made [2].

A common concern for patients with BWS is cancer development [5]. Up to 8% of all BWs patients develop an embryonal tumor during their early childhood, but the exact tumor risk ranges from 1% to 30% depending on the precise causative genetic/epigenetic alteration [7]. The most common types of tumors are WT (52%), hepatoblastoma (14%), neuroblastoma (10%), rhabdomyosarcoma (5%), and adrenal carcinoma (3%). The overall cancer risk is highest in the first 2 years of life, and the cancer risk then declines progressively before puberty, approaching the cancer risk of the general population. Currently, there is no evidence of an increased risk of malignant tumors in adulthood [6].

Children with BWS and WT tend to be considerably younger at the time of WT onset and present with less metastatic disease and fewer anaplastic tumors [3]. This might be due to US screening for children with BWS [3]. Although the overall survival is similar with sporadic WT, BWS-associated WT have a smaller size amenable to less-intensive chemotherapy, a lower need for radiotherapy, and are manageable with nephron-sparing surgery, which is preferred given the increased co-occurrence of bilateral WT from diffuse nephrogenic rests [3,7].

Abdominal US is the initial imaging modality in suspected WT [6]. MRI remains the primary cross-sectional imaging technique, which allows a better assessment of NRs and their distinction from malignant tumors. In this regard, the most useful MRI sequences are diffusion-weighted imaging and contrast-enhanced T1-weighted imaging. NRs are best visualized on T1-weighted imaging, with a hypo-intense appearance and a homogeneous signal after contrast [3]. CT is not primarily indicated due to a low specificity for distinguishing NRs from WT and the risk of radiation exposure, which must be avoided, especially in syndromic patients [3]. Typical radiologic patterns allow preoperative chemotherapy to be started without a biopsy in most cases, which is also true for our patient. Antenatal US can reveal features suggestive of BWS that may warrant prenatal molecular diagnostic testing. Omphalocele is the most common finding and macroglosia and placentomegaly are the most predictive findings on US [11,13,14].

Various protocols have been suggested for tumor surveillance in BWS, usually comprising abdominal US with or without measurement of AFP levels at various ages and intervals during childhood [2]. Although the actual risk and type of tumor depend on the genetic defect, the American Association for Cancer Research recommends abdominal US screening for all cases of BWS. US examination is recommended to screen for WT every 3-4 months from diagnosis until 7-8 years of age, which allows 95% case detection [3,4,7]. A longer renal surveillance by US may be warranted if unilateral or bilateral nephromegaly, cystic changes, or duplication of the collecting system are seen.

For hepatoblastoma, abdominal US every 3 months from diagnosis to the age of 4 years with or without serum AFP is recommended [4,6,7]. No specific surveillance is provided for rhabdomyosarcoma; however, the serial abdominal US recommended for the first 4 years of life can assist in the early detection of rhabdomyosarcoma as well [4].

Conclusion

BWS is a childhood cancer predisposition disorder that requires a molecular genetic test for disease confirmation and the formulation of a prognosis. In resource-limited settings, clinical criteria can be of paramount importance to diagnose WBS since approaches to management of complications such as WT differ considerably in syndromic vs nonsyndromic cases.

Authors' contributions

All authors contributed to the conduct of this research and read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The data supporting the findings of the case are available upon request to the corresponding author.

Patient consent

Written informed consent was obtained from the patient's parents for anonymized patient information to be published in this article.

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