Case Report

A Rare Cause of Hemi-Hypertrophy: Bannayan-Riley-Ruvalcaba Syndrome – Case Report and Review of Literature

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Abstract

Background: Bannayan–Riley–Ruvalcaba syndrome (BRRS) is a rare autosomal dominant disorder within the PTEN hamartoma tumor syndrome spectrum, classically characterized by macrocephaly, developmental delay, intestinal hamartomatous polyps, lipomas, and mucocutaneous pigmentation. Although generalized overgrowth is a recognized feature in BRRS, asymmetric overgrowth or hemi-hypertrophy is an uncommon and under-reported manifestation, often leading to diagnostic confusion with other overgrowth syndromes. **Case Presentation:** We report the case of a 14-year-old male with intellectual disability who developed progressive asymmetric overgrowth involving the left upper and lower limbs, associated with facial asymmetry. Further evaluation revealed macrocephaly, gastrointestinal hamartomatous polyps, lipomatous and vascular cutaneous lesions, and dilated superficial veins. Entities within the overgrowth syndrome spectrum were considered, and genetic testing was done to confirm the diagnosis of BRRS. **Conclusion:** This case captures an unusual overgrowth pattern that is rarely discussed in the literature, as evidenced by our review. Early identification and genetic testing are crucial for guiding surveillance of related cancers and for providing appropriate genetic counseling to the patients.

Keywords: Bannayan-Riley-Ruvalcaba Syndrome, Hemi-Hypertrophy, Asymmetric Overgrowth, PTEN, Case Report.

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Introduction

Hemi-hyperplasia (or hemi-hypertrophy) is a presentation seen in the spectrum of overgrowth syndromes characterized by asymmetric or segmental overgrowth of body parts. These conditions can present as isolated findings or as components of well-defined genetic syndromes. The clinical significance of identifying these conditions extends beyond cosmetic concerns, as many are associated with increased risks of embryonal tumors. We present a case of a 14-year-old male with intellectual disability who progressively developed asymmetric hypertrophy years after birth. Our literature review highlights the rarity of this presentation among BRRS patients.

Case Presentation

A 14-year-old male was brought to our institution with the chief complaint of asymmetric body growth. The child was apparently normal up to age 5, after which the parents noticed a difference in the extremity girth, greater on the left side. This difference in limb girth has become more prominent as the age has progressed.

Natal history is significant for increased birth weight and length (both above the 90th percentile). He had attained the developmental milestones appropriate for his age. No family history of similar complaints or inherited diseases was noted. Examination of the patient revealed significant facial asymmetry, increased muscularity of the left upper and lower limbs, and increased size of the left foot [Figure 1]. Anthropometric assessment [Table 1] revealed macrocephaly (above 99th percentile) and increased limb girths on the left side of the body. Cardiopulmonary and neurological assessments were unremarkable.

The patient was noted to have a ‘low-average’ intelligence (Composite Score: 86) according to the WISC-V classification. A thorough head-to-foot examination revealed skin hemangiomas over the trunk, dilated veins over the lateral aspect of the left thigh, and enlargement of the testes and scrotal sac. Baseline blood investigations showed microcytic hypochromic anemia (hemoglobin: 10 g/dL, hematocrit: 31%). Blood glucose, thyroid function tests, liver function tests, renal function tests, and electrolyte levels were within normal limits. Computed tomography of the abdomen, chest, spine, and brain turned out to be normal. An arterial and venous Doppler study of both lower extremities was performed to rule out arteriovenous malformations and revealed no significant abnormality. Electrocardiogram and echocardiography were performed to rule

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out cardiac involvement; both were unremarkable.

Considering the clinical features and the age of presentation, a clinical suspicion of overgrowth syndromes was raised, and the patient was referred to the genetics department for further evaluation. Genetic testing and karyotyping were performed to narrow down the underlying anomaly. On genetic assessment, a pathogenic mutation in the PTEN gene was identified at 10q23.3, supporting the diagnosis of Bannayan-Riley-Ruvalcaba Syndrome and ruling out related syndromes.

Cancer screening was performed due to the associated risk. Colonoscopy revealed multiple small nodules in the terminal ileum. Histopathological examination of the nodule revealed hamartomatous polyps. Ultrasound study of the kidneys and thyroid gland was unremarkable. Genetic counselling was advised to provide knowledge about the nature of the disease, and the child has been on regular follow-up at our institution for the past seven years. Periodic tumor screening has been performed over the years. The patient appears well during office visits and has not faced any hindrance to daily activities. No evidence of malignancy has been detected as of this date.

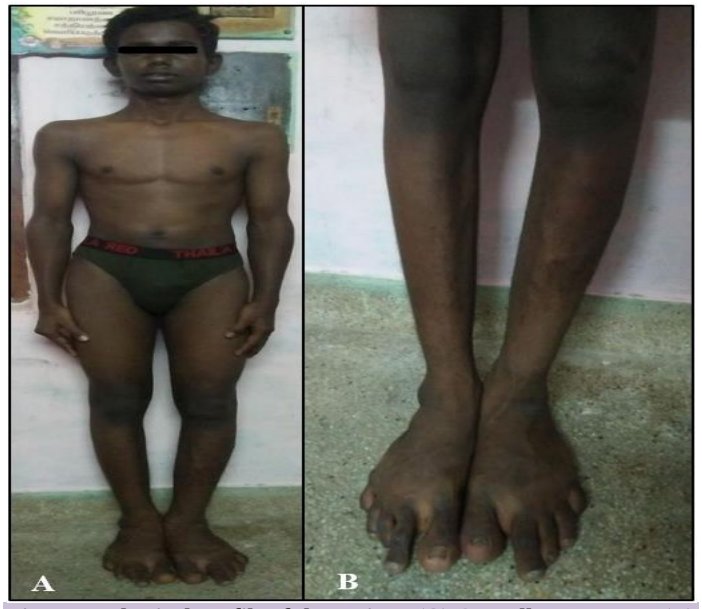

Figure 1: Physical profile of the patient. (A) Overall appearance (B) Enlarged left foot.

Table 1: Anthropometric Measurements of the Patient

Parameters	**Measurements**	
Height	162 cm	
Weight	48 kg	
Body mass index	18.29 kg/m2	
Head circumference	61 cm	
Limb Measurements	**Right (cm)**	**Left (cm)**
Mid-arm circumference	20	22.5
Mid-forearm circumference	15	17
Mid-thigh circumference	31	33.5
Mid-leg circumference	28	29.5

Table 2: Comparison of Hyperplasia Patterns among Overgrowth Syndromes

Syndrome	**Symmetry**	**Age of Onset**	**Progression**	**Distribution Pattern**	**Genes Involved**	**Key Associations**
Isolated hemi-hyperplasia (most common)	Asymmetric	At birth	Non-progressive	One side of body	Sometimes 11p15 abnormalities	Isolated hemi-hyperplasia without other syndromic features. Increased embryonal tumor risk (Wilms tumor, hepatoblastoma)
Beckwith–Wiedemann syndrome	Generalized or hemi-hyperplasia	At birth	Growth normalizes later	Generalized	11p15 imprinting defects (IGF2/H19 region)	Neonatal hypoglycemia, omphalocele, macroglossia. Increased risk for Wilms tumor and hepatoblastoma
Proteus syndrome	Markedly asymmetric	Early childhood (not obvious at birth)	Progressive	Patchy, mosaic	AKT1 (somatic)	Cerebriform connective tissue nevus, skeletal deformity, lipomas. Risk for deep vein thrombosis and mixed vascular malformations
Klippel–Trénaunay syndrome	Asymmetric (usually 1 limb)	At birth	Stable/slow	Usually single limb (lower limb common)	Often PIK3CA (somatic)	Port-wine stain, venous varicosities, limb length discrepancy, chronic venous insufficiency
CLOVES syndrome	Asymmetric	At birth	Congenital; proportional growth	Truncal predominance	PIK3CA (somatic)	Large lipomatous masses, epidermal nevi, spinal and skeletal anomalies, complex vascular malformations
Neurofibromatosis type 1	Usually asymmetric if overgrowth present	Early childhood	Slowly progressive	Segmental or generalized	NF1	Café-au-lait macules, axillary freckling, optic glioma, plexiform neurofibroma, vascular dysplasia
Cowden syndrome	Symmetric	Childhood–	Non-	Generalized	PTEN	Macrocephaly, mucocutaneous

		adolescence	progressive			papillomas, trichilemmomas. Increased risk for breast, thyroid, endometrial cancers.
Bannayan–Riley–Ruvalcaba	Usually symmetric	At birth/infancy	Non-progressive	Generalized	PTEN	Macrocephaly, developmental delay, intestinal hamartomas, lipomas, penile lentigines. Risk for breast, thyroid, endometrial, renal, colorectal cancers.

Table 3: Literature Review of Cases of Bannayan-Riley-Ruvalcaba Syndrome (BRRS) Presenting with Asymmetric Overgrowth

Case Report	Age/Sex	Clinical Presentation	Progression	Malignancies Associated	Remarks
Ghusayni et al. (2018) [8]	11/M	Macrocephaly, developmental delay, athetotic quadriplegic cerebral palsy with left hemi-megalencephaly evident early, later macrocephaly and other BRRS features	Chronic symptoms with persistent neurologic disability	None reported	Hemi-megalencephaly without Proteus criteria, PTEN mutation identified, underscores asymmetric brain/body overgrowth in BRRS
Li et al. (2024) [9]	28/M	Macrocephaly, diffuse hamartomas, delayed speech, large varicosities/arteriovenous malformations (AVM) in right arm and chest	AVMs present since childhood, worsened but not disabling	None identified	BRRS with arteriovenous malformations, highlighting vascular asymmetry in rare BRRS cases
Present Case	14/M	Macrocephaly, intestinal polyps, lipomatous features, hemangiomas, dilated veins, and hypertrophy of left-sided extremities with facial asymmetry	Gradually more prominent asymmetry but non-destructive	No malignancy, surveillance ongoing	PTEN gene variant confirmed, atypical but documented asymmetric overgrowth

Discussion

The clinical presentation of hemi-hypertrophy in the context of BRRS poses a significant diagnostic challenge, as asymmetric overgrowth is a hallmark of several overlapping overgrowth syndromes. Asymmetric overgrowth can present as an isolated finding (most common) or as part of syndromic associations such as Beckwith-Wiedemann syndrome, Proteus syndrome, Klippel-Trenaunay syndrome, CLOVES syndrome, neurofibromatosis type 1, Cowden syndrome, or, rarely, BRRS. Overgrowth syndromes vary in onset, symmetry, progression, distribution, and associated features, aiding clinical differentiation.[1,2] [Table 2] provides a comparison of growth patterns among these entities.

BRRS is a rare cause of asymmetric overgrowth. Classical presentation includes multiple hamartomas in various organs, macrocephaly, developmental delay, and penile lentigines. The prevalence of BRRS is estimated to be less than 1 in 200,000 people.[3] BRRS is caused by mutations in the PTEN gene, which encodes a tumor suppressor protein that regulates cell growth, survival, and migration.[4] PTEN is involved in the PI3K/AKT/mTOR signaling pathway, which controls various cellular processes such as metabolism, proliferation, differentiation, and apoptosis. Mutations in PTEN lead to hyperactivation of this pathway, resulting in increased cell growth and survival, and reduced apoptosis. This leads to the formation of hamartomas and increases the risk of malignancy across various tissues.

In BRRS, the pattern of hyperplasia is usually symmetric, non-progressive, generalized, and non-distorting, with marked macrocephaly and hamartomatous and lipomatous tissue proliferation. BRRS better explains the clinical features of our patient than other overgrowth syndromes. In Proteus Syndrome, the overgrowth is typically distorting, progressive, and follows a mosaic distribution.[5] In contrast, this patient's limb asymmetry was characterized by increased muscularity and girth of one side rather than severe skeletal distortion of the opposite side. Furthermore, the dilated veins over the lateral thigh and skin hemangiomas could easily raise suspicion for Klippel-Trénaunay syndrome.[2] However, the absence of arteriovenous malformations on Doppler studies and the presence of macrocephaly are strong negative predictors for this. The presence of macrocephaly, gastrointestinal hamartomas, and positive genetic testing favors BRRS as the diagnosis. However, only a handful of cases have reported an asymmetric pattern of overgrowth in BRRS.

We conducted a comprehensive review of the literature to identify cases of BRRS presenting with asymmetric overgrowth. Electronic databases, including PubMed, Scopus, and Web of Science, were systematically searched from database inception through February 2026. The search strategy used a combination of MeSH terms and free-text terms including – 'Bannayan–Riley–Ruvalcaba syndrome', 'BRRS', 'PTEN hamartoma tumor syndrome', 'hemihypertrophy', 'hemihyperplasia', 'asymmetric overgrowth', and 'segmental overgrowth'. Boolean operators and truncations were used to refine results. A total of 16 studies were obtained through this search.

Eligible studies included case reports, case series, cohort studies, and observational studies describing individuals with clinically or molecularly confirmed BRRS and documented hemihypertrophy or asymmetric overgrowth. Articles were included if published in English. Reviews without original patient data, conference abstracts lacking sufficient clinical detail, and studies describing other PTEN-related conditions without specific BRRS phenotyping were excluded unless individual-level data could be extracted. Two independent

reviewers (H.S., P.S.) screened titles and abstracts for eligibility, followed by full-text assessment. Reference lists of included articles were manually screened to identify additional relevant publications. Due to the rarity of BRRS with hemihypertrophy and the predominance of case-based literature, only a qualitative synthesis was performed, and a formal risk-of-bias assessment was not conducted. [Table 3] shows the results of the literature review.

The clinical course and complications of BRRS depend on the type and location of the hamartomas, as well as the risk of malignancy. Some patients with BRRS may have a normal life expectancy and quality of life, while others may have reduced survival and significant morbidity. Some of the possible complications of BRRS include – intestinal obstruction or perforation, increased intracranial pressure or seizures due to ventriculomegaly, hydrocephalus or brain tumors, hemorrhage or infection due to bleeding or ulceration of hemangiomas, thyroid cancer or thyroid dysfunction due to thyroid nodules, and a heightened risk for breast cancer and renal cell carcinoma.[6]

Periodic cancer screening and a multi-disciplinary approach are necessary for the management of BRRS. The cancer screening protocol parallels that of the other entities in the PTEN hamartoma spectrum.[7] Annual thyroid ultrasonography should be done starting from the age of diagnosis. In female patients, clinical breast exam (starting at 18 years) every 6-12 months and annual mammogram (starting at age 30) is recommended for breast cancer screening. Endometrial biopsy every 1-2 years and transvaginal ultrasound could be considered for endometrial cancer assessment. Colonoscopy must be performed every 5 years starting at age 35, and more frequently if symptoms are present or polyps are noted. Renal ultrasound is advised from age 40, every 1-2 years, to screen for renal malignancy.[7] Close follow-up with a pediatrician from the time of diagnosis is recommended to assess developmental status in children. Due to its autosomal dominant inheritance, genetic counselling and screening of family members may be considered.[8,9]

Conclusion

This case demonstrates that asymmetric overgrowth, while rare, is a possibility in BRRS patients. However, such patients present with the other classical features suggestive of the association. BRRS must thus be included in the differential diagnosis for asymmetric hyperplasia. Genetic testing is essential for diagnosis. As BRRS is associated with multisystem hamartomatous involvement and an increased lifetime risk for cancer, early diagnosis, multi- disciplinary management, and periodic tumor screening can prove to be beneficial.

Patient perspective: "Being informed about the risks and nature of my disease has enabled me to actively seek medical care and be wary of the potential complications I might face."

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Conflicts of interest

There are no conflicts of interest.

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