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The complexity of phosphatase and tensin homolog hamartoma tumor syndrome: A case report

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Abstract

Germline pathogenic variants found in the phosphatase and tensin homolog gene are associated with a range of rare syndromes that collectively fall under the umbrella of phosphatase and tensin homolog hamartoma tumor syndromes. Due to the wide array of possible clinical presentations and the varying degrees of symptom severity, many individuals with phosphatase and tensin homolog hamartoma tumor syndromes might remain undiagnosed for an extended period. We describe a case of a male child who received the diagnosis at the age of 12. His clinical features included macrocephaly, hypertrophy in the left arm, thyroid nodules, penile freckles, developmental delay, and an autism spectrum disorder. Whole exome sequencing revealed a de novo heterozygous variant in the phosphatase and tensin homolog. The case highlights the diverse and complex nature of phosphatase and tensin homolog hamartoma tumor syndromes, emphasizing the necessity for early diagnosis, multidisciplinary care, and surveillance protocols, offering the potential for improved prognostic outcomes and enhanced quality of life for affected individuals.

Keywords

PTEN, PHTS, macrocephaly, hemihypertrophy, penile freckles

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Introduction

PTEN hamartoma tumor syndrome (PHTS) represents an autosomal dominant condition characterized by extensively variable clinical features affecting multiple organ systems.[1] It encompasses a number of historical clinical presentations including Cowden syndrome (CS), Bannayan–Riley–Ruvalcaba syndrome (BRRS), proteus and proteus-like syndrome, autism spectrum disorders (ASD) with macrocephaly, juvenile polyposis of infancy, and adult Lhermitte–Duclos syndrome.[2,3] Frequently described clinical findings are developmental delay (DD), macrocephaly, skin lesions, thyroid pathologies, gastrointestinal hamartomas, and breast cancer (BC).[4] All of the above-mentioned syndromes are linked to pathogenic variants in the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene on chromosome 10q23 (OMIM 601728). The *PTEN* gene is an important tumor suppressor gene that plays a critical role in the molecular mechanisms regulating cell migration, proliferation, and apoptosis. PTEN protein dephosphorylates phosphatidylinositol (3,4,5) triphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2), antagonizing the downstream pathways of receptor tyrosine kinases and phosphatidylinositol-3-kinase (PI3K). PTEN inhibits the PI3K-Akt and mammalian target of rapamycin (mTOR) signaling pathways.[5] Reduced PTEN activity causes increased phosphorylation of various cell proteins, affecting processes of cell growth, migration, and death.[6] Overactivation of the PI3K/AKT/mTOR pathway can result in the formation of benign and malignant tumors and overgrowth.[6] Individuals with PHTS are at significant risk for

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malignancies and the most commonly involved organs are the breast, endometrium, and thyroid.[4,7]

No definitive evidence exists to indicate differences in the frequency of various types of cancer in the different *PTEN*-associated syndromes or a particular genotype–phenotype correlation.[3] Recent literature review by Rahmatinejad et al. demonstrated that PHTS cases involving individuals under 18 are rare.[4] Hence, it is important to report cases of PHTS in this age group to better characterize clinical findings and prognosis. Here, we describe a case of PHTS in a 12-year-old boy. Detailed descriptions of clinical manifestations and diagnosis are presented.

Case presentation

A 12-year-old boy was referred for genetic evaluation due to congenital macrocephaly, DD, and progressive hypertrophy of the left arm. He was born to a healthy mother at 39 weeks of gestation by cesarean section. The pregnancy and delivery were uneventful. His birth weight was 3400 g (54th percentile) and his length was 49 cm (32nd percentile). Prenatal ultrasound revealed hydrocephalus from 30th weeks of gestation and his occipitofrontal circumference measured 41 cm (>99th percentile) at birth. Brain magnetic resonance imaging performed at 6 months showed compensated hydrocephalus. Motor development progressed normally. His language acquisition was delayed and at 3 years he was diagnosed with ASD. He had learning difficulties at school with particular challenges of expressive verbal skills but very good calculation skills and memory.

At the age of 5, progressive hypertrophy of the left arm was evident which necessitated surgery at the age of 7. The biopsy results confirmed the presence of a hamartoma with vascular and myxoid lipomatous elements. Hypertrophy in the left ulnar region continued, causing discomfort, episodic pain, and limiting mobility. By the age of 11, palpable thyroid nodules emerged. Fine-needle aspiration cytology reported follicular neoplasm category IV (The Bethesda System for Reporting Thyroid Cytology—TBSRTC).[8]

Physical examination revealed macrocephaly (Head circumference—63 cm, 97th percentile). Remarkably, multiple penile freckles were observed upon genital examination (Figure 1). The left arm appeared hypertrophic. Mild scoliosis was present. During the neurological examination, the patient was alert, oriented, and cooperative throughout the assessment. The patient demonstrated age-appropriate memory, attention deficit, and mild dysarthria. Cranial nerve examination showed intact functions, including normal visual acuity, pupillary responses, and coordinated extraocular movements. The motor system assessment demonstrated limited elbow, wrist, and finger extension, as well as difficulty grasping objects with the affected limb. Sensory examination revealed decreased sensation to pinprick in the affected limb and mild pain sensation upon deep palpation in the hypertrophic area. Deep tendon reflexes were brisk and symmetrical, and the plantar reflex exhibited a flexor response. Coordination and balance testing showed no abnormalities. The patient's gait was steady and balanced. Abdominal and testis ultrasound was normal. Colonoscopy revealed less than 20 hamartomatous polyps in the rectum and sigmoid.

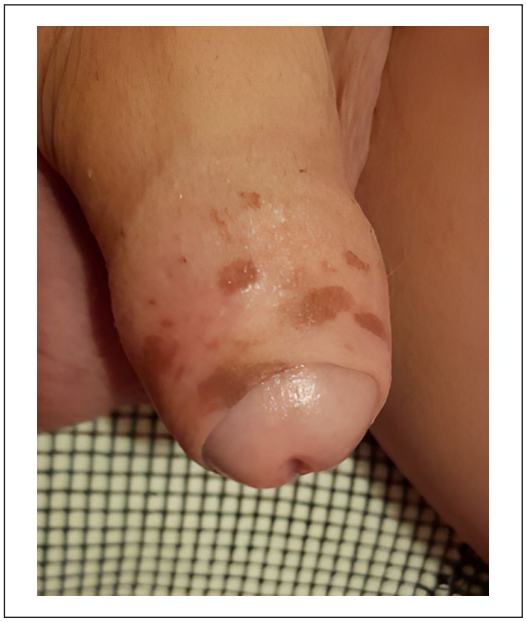

Figure 1. Multiple pigmented macules on the penile shaft.

Whole exome sequencing (WES) confirmed a de novo heterozygous variant, c.388C>T, p.Arg130, in the *PTEN* gene (NM_000314.4), classified as pathogenic.[9] Considering the clinical manifestations and WES results, PHTS was diagnosed. Annual comprehensive physical examination, yearly dermatological examination, yearly abdominal and testis ultrasound, and colonoscopy every 5 years were recommended.

The patient was referred to the surgical oncology department for the management of thyroid findings and further management of left-hand hypertrophy. A long-term follow-up is underway.

Discussion

CS and BRRS are the most frequently described entities caused by pathogenic variants in the *PTEN* gene. These syndromes may be viewed as a single condition with variable expression and age-dependent penetrance.[10] According to the latest recommendations when a *PTEN* pathogenic variant is found, the gene-related name, PHTS, should be used.[1] The National Comprehensive Cancer Network issued recommendations for the diagnostic criteria of PHTS, defining major and minor diagnostic criteria.[11] If three major criteria or a combination of two major and three minor criteria are met, or in instances of a familial case meeting two major or one major and two minor criteria, the recommendation is to commence molecular testing to detect *PTEN* mutations. Importantly, penile freckling is a well-known feature in

PTEN-positive BRRS patients documented in 67%–85% of cases.[12] In a retrospective study by Tan and colleagues, penile freckling was present in 13/23 PHTS patients.[13] In the German pediatric guideline, Plamper et al. suggest a modified diagnostic algorithm for children and adolescents with *PTEN* mutations. This diagnostic algorithm covers all specialties that provide care for children.[3]

Pathogenic c.388C>T (p.Arg130*) variant detected in our patient is consistent with heterogeneous clinical findings reported in the literature[14] and has been reported in numerous individuals diagnosed with CS, BRRS, malignancies, and/or other clinical features associated with *PTEN* mutations. This variant induces an early termination codon and is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on existing information, this variant represents a well-known pathogenic variant.

Individuals with PHTS have a significantly increased lifetime risk of developing malignancies. In the study by Hendricks et al., a European adult PHTS cohort of 455 patients was analyzed to provide more accurate and personalized cancer risks associated with PHTS. The results, based on a median follow-up of 6 years, indicate that by age 60, PHTS-related cancer risk is much higher in females (68.4%–86.3%) than in males (16.4%–20.8%). The study highlights the importance of considering *PTEN* germline variants, revealing twofold to threefold increased risks for BC in *PTEN* truncating variants and approximately twofold increased risks for phosphatase domain variants. The primary focus for surveillance is recommended to be on BC (in females), endometrial cancer, and thyroid cancer.[7]

Our patient presented with DD and macrocephaly. WES was performed based on the American College of Medical Genetics guidelines, which recommends it as a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders.[15] The presented case emphasizes the clinical utility of WES in the context of DD and highlights diverse clinical manifestations of PHTS in a juvenile boy exhibiting macrocephaly, left arm hypertrophy, thyroid nodules, penile freckles, along with DD, and ASD. These manifestations emphasize the importance of a comprehensive diagnostic approach, integrating detailed clinical assessments, imaging studies, and genetic testing for precise syndrome delineation.

Further studies are needed to refine diagnostic criteria and management strategies to establish evidence-based cancer surveillance recommendations for patients with PHTS.

Conclusion

We reported a case of PHTS in a 12-year-old boy exhibiting macrocephaly, left arm hypertrophy, thyroid nodules, penile freckles, DD, and ASD. This case reinforces the important role of integrated approaches, combining clinical assessments, genetic testing, and ongoing monitoring, to achieve accurate syndrome delineation and develop tailored management options.

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Author's contribution

T. T. examined and cared for the patient. K. B., T. T., S. J., and S. M. R. wrote the manuscript. The ultimate submitted version of the manuscript was reviewed and endorsed by all of the co-authors.

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Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

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