

Macroductyly as the Presenting Finding for a Complex Genetic Disorder

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Introduction

Macroductyly is the congenital enlargement of one or more digits due to overgrowth of the soft tissue and/or underlying bone. It is a rare malformation, with an overall incidence of 1 in 100,000 live births [1]. Macroductyly may occur as an isolated finding or represent one manifestation of a generalized disorder, such as Beckwith Wiedemann Syndrome (BWS), *PIK3CA*-Related Overgrowth, Proteus Syndrome (PS), Neurofibromatosis Type 1, Klippel-Trénaunay syndrome (KTS), or Fibrodysplasia Ossificans Progressiva [2]. Identifying an underlying cause can have significant implications for the care of the affected digit as well as the overall health of the patient. For example, patients with a *PIK3CA* pathogenic variants are at risk for excessive and abnormal scarring with their surgical repair [3], while children with BWS require surveillance for several types of embryonic tumors [4]. While the diagnosis of the underlying condition can often be reached based on clinical findings, the phenotypic differences may be subtle and may not be apparent in very young children. Here we report one such case, a child with apparently isolated macroductyly that had a complex etiology identified through genetic testing. This case demonstrates the essential role of genetics evaluation and testing in the care of these children.

Case Report

A 19-month-old male presented for genetic evaluation for an enlargement of the right thumb and forearm. The size difference was first recognized in the thumb at approximately 12 months by his parents. His pregnancy and past medical history were unremarkable. He was otherwise healthy, with normal growth and development.

On initial evaluation, the child's right thumb was noticeably larger than his other digits (Figure 1). The remaining right-hand digits were normal in appearance, but were slightly larger than those on the left. The right forearm had a larger circumference than the left. He was otherwise non-dysmorphic, and his lower limbs were normal in appearance and symmetric. X-rays of the right upper extremity revealed no significant bony abnormalities. Renal and hepatic ultrasounds were normal, demonstrating no masses or organomegaly.



Due to the clinical suspicion for BWS, methylation and copy number analysis of 11p15 and sequencing of *CDKN1C* was ordered on peripheral blood. These returned normal results.

Subsequently, a tissue biopsy was obtained from the affected area to test for somatic alterations in fibroblasts, including re-testing for BWS as well as other genes associated with overgrowth syndromes. This testing identified a mosaic pathogenic variant in *PIK3CA* (c.3140A>T; p.H1047L) consistent with a diagnosis of *PIK3CA*-related segmental overgrowth.



On re-examination 6 months later, the clinical appearance of the affected extremity was now consistent with that seen in *PIK3CA*-related segmental overgrowth. Over the next two years, the relative size and affected area modestly increased. At 32 months, the hemi-hyperplasia extended proximally to the biceps and shoulder region (Figure 2). During this time, progressive impairment in dexterity and function of the patient's affected hand was observed. The patient has also shown an increased preference for using his unaffected hand.

Discussion

Here we report a case of macroductyly due to a somatic alteration in *PIK3CA*, consistent with the diagnosis of *PIK3CA*-related segmental overgrowth. This was accomplished through a clinical genetic evaluation, but the diagnosis was confirmed using Next-generation genetic testing. This testing allowed for an earlier diagnosis than would have been possible by clinical evaluation alone, as there is a wide differential for the early identification of macroductyly. This case illustrates the benefits of a multidisciplinary approach, including genetic evaluation, to children with macroductyly and hemi-hyperplasia. In this case, the phenotype of the affected digit did not exhibit the characteristics that would suggest *PIK3CA*-related segmental overgrowth at the time of initial evaluation. Diagnosis was only possible through genetic testing of the affected tissue, as causative mutations in *PIK3CA*-related segmental overgrowth are somatic and limited to the affected tissue. Therefore, tissue biopsy is required to obtain

the tissue and identify the mutation, and therefore make the correct diagnosis.

Due to the phenotypic overlap of these conditions in young children, genetic testing is the only reliable means to diagnosis as early as possible for the patient with macroductyly and hemi-hyperplasia. For patients with similar presentation, considering genetic referral is crucial given the concomitant findings in syndromes associated macroductyly. Early identification of a genetic mutation will expedite patient referral to the appropriate service and optimize patient care. While macroductyly alone is not a syndrome-defining feature, it can be part of an overgrowth syndrome that warrants further genetic workup [2]. The clinical workup for a child with macroductyly requires ruling out several syndrome including BWS, more severe forms of the *PIK3CA*-related overgrowth spectrum such as CLOVES (Congenital Lipomatous Overgrowth, Vascular Malformations, Epidermal Nevi, Scoliosis/Skeletal and Spinal) syndrome, the related MCAP (Megalencephaly-Capillary Malformation) syndrome, and Klippel-Trenaunay syndrome.

BWS is an overgrowth disorder found in 1 out of 13,700 births [5] comprised of one or more of a spectrum of clinical findings including neonatal hypoglycemia, macrosomia, macroglossia, omphalocele, and ear creases or pits. Affected individuals are at increased risk for developing malignant and non-malignant tumors. Patients should be screened in childhood for embryonal tumors such as Wilms tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma. BWS often have visceromegaly, as well as adrenal and renal abnormalities [6]. Regions and/or tissues of the body affected with hemihyperplasia may vary, however growth rates tend to slow by age 8, and hemihyperplasia can become less apparent over time [7]. Patients with BWS tend to have normal intelligence and life expectancy [8].

MCAP syndrome is characterized by megalencephaly or hemimegalencephaly, as well as abnormalities of muscle tone, seizures, and varied levels of intellectual disability. Patients also tend to have cutaneous capillary malformations, connective tissue dysplasia, and focal or generalized somatic overgrowth digital anomalies such as syndactyly and polydactyly [9]. Along with neurosurgical monitoring for hydrocephalus, children with MCAP syndrome must be screened for Wilms tumor and central nervous system tumors (meningiomas) [10]. CLOVE syndrome, found in less than 1 in 1,000,000 live births [11], is characterized by a congenital lipomatous asymmetric overgrowth of the trunk, lymphatic system, vascular malformations, epidermal nevi, and skeletal anomalies (scoliosis, wide hands and feet, macroductyly) [9]. Unlike MCAP, CLOVES syndrome has more prominent growth dysregulation with complex lipomatous tissue overgrowth (typically manifesting as a truncal lipomatous mass) along with combined lymphatic and vascular malformations [9].

Klippel-Trenaunay syndrome (KTS) is characterized by a triad of findings: port-wine stain, varicosities, and connective tissue hypertrophy involving an extremity (usually a leg, digital findings are far less common). Patients with KTS are predisposed to deep vein thrombosis and cellulitis in the setting of lymphedema [12].

While these conditions are clinically distinct, with different prognoses and risks for associated medical concerns, they can be difficult to diagnose in young children based solely on clinical findings. Further complicating matters are the recent advances in genetic knowledge and testing technologies. It is important for hand surgeons to be aware of the wide differential diagnosis for macroductyly and recognize the importance of a thorough genetics evaluation to identify potential syndromic causes as this will impact therapeutic options and long-term management. It also highlights the importance of obtaining a fibroblast sample for genetic testing, which can be performed at the same time as orthopedic surgical procedures.

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