Tuberous Sclerosis Complex Associated with Heterotopic Ossification in a Young Girl

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1. Introduction

Tuberous sclerosis complex (TSC) is a multisystem disorder resulting in hamartomatous lesions. Despite diverse manifestations, skeletal muscular comorbidity is rarely reported in TSC. We report a 2-year-old girl with TSC who suffered from multiple subcutaneous masses over the paraspinal and bilateral scapular areas, which caused disabling pain on any passive movement. Three-dimensional computed tomography scanning revealed multiple calcifications that were consequently diagnosed as fibrodysplasia ossificans progressiva. Such imaging features should be evaluated cautiously to avoid unnecessary surgical intervention and biopsy that may worsen the condition.

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Key Words
fibrodysplasia ossificans progressive; heterotopic ossificans; tuberous sclerosis complex

TSC can be caused by mutations in either the TSC1 gene on chromosome 9q34 encoding hamartin or the TSC2 gene on chromosome 16p13.3 encoding tuberin. Hamartin and tuberin function as a complex that is involved in the control of cell growth and cell division. Thus, mutations at the TSC1 and TSC2 loci result in a loss of control of cell growth and cell division, and therefore a predisposition to forming hamartomas.2,3

Fibrodysplasia ossificans progressiva (FOP) is a severely disabling disorder of connective tissue characterized by progressive heterotopic ossification (HO) that forms qualitatively normal bone in characteristic extraskeletal sites.4
Soft tissue ossification is the characteristic radiographic feature of FOP, and radiographic and bone scan findings suggest normal modeling and remodeling of heterotopic bone.\(^5\) Computed tomography and magnetic resonance imaging of early lesions have been described,\(^6,7\) and the definitive diagnosis of FOP can be made by simple clinical evaluation of progressively ossifying soft tissue lesions.\(^8\) To the best of our knowledge, so far no study has described TSC in association with HO.

2. Case Report

A 2-year-old girl was born to nonconsanguineous healthy parents. She was diagnosed with an intracardiac mass prenatally, and overt multiple hypomelanotic patches were noted after birth. Brain magnetic resonance imaging revealed cortical tubers and subependymal nodules, which were evidence of TSC. On follow-up, she was noted to have had a complex partial seizure at 8 months of age and global developmental delay in infancy. At 2 years of age, she suffered from multiple subcutaneous masses over the paraspinal and bilateral scapular areas, which caused disabling pain on any passive movement for 1 month. It was characterized as firm, immovable flare-up without any limitation in joint movement. The descriptive pattern of ongoing pain was limited possibly due to her global developmental delay and young age. Initial magnetic resonance imaging of muscles showed moderate inhomogeneous masses and a high signal over the affected areas (Figure 1). Excisional sections of muscle biopsy, which were obtained from the mass over the affected area, as specimens were stained with hematoxylin and eosin. The pathologic report of the biopsy showed neurofibers admixed with adipose tissue. Routine laboratory tests, including biochemical evaluations of bone mineral metabolism, were normal. A subsequent three-dimensional computed tomography scan, performed because of ongoing pain, revealed multiple calcifications that were consequentially diagnosed as FOP (Figure 2). She was managed palliatively with Chinese herbs for the intramuscular calcification.

3. Discussion

Both TSC and FOP are rare genetic disorders; however, no gene locus is shared by these two diseases. The diagnosis is based on the presence of major and/or minor features of the diseases. Despite variable and multisystem manifestations, muscular complications of TSC are rare, particularly in the musculoskeletal system.\(^9\) Only a limited number of articles have reported muscular lesions in TSC involving the primary smooth and cardiac muscles, including renal angiomyolipomas, pulmonary lymphangiomyomatosis, and rhabdomyomas. To date, skeletal muscular comorbidity has not been reported.

HO is a severe, rare condition of the skeletal muscles, mostly seen in FOP. It is commonly misdiagnosed, as clinicians often fail to associate the rapidly developing soft tissue swellings that appear on the head, neck, and upper back with malformed great toes.\(^10\) The correct diagnosis of FOP can be made clinically prior to observing radiographic features of HO if rapidly waxing and waning soft tissue lesions are associated. In the absence of such associations, FOP is commonly misdiagnosed.\(^11\) The pathophysiology of...
TSC and FOP is different. FOP is multifocal, usually starting to develop after traumatic injury.\textsuperscript{12} It is supposed to result from dysregulated bone morphogenetic proteins, which are members of the transforming growth factor-beta superfamily and play a role in the development of bone and other tissues.\textsuperscript{13}

Medical intervention for FOP is supportive and palliative. Guidelines for symptomatic management of disease highlight the anecdotal utility of glucocorticoids and non-steroidal anti-inflammatory drugs in managing chronic discomfort and ongoing flare-ups.\textsuperscript{14} Surgical release of joint contractures is generally unsuccessful and risky for new trauma-induced HO, and osteotomy or surgical removal of heterotopic bone to mobilize joints will generally cause the development of additional HO at the operative site.\textsuperscript{15} Repetitive trauma is the most important exacerbating factor of the disease; therefore, avoiding unnecessary trauma or surgical procedure can minimize originating or exacerbation of the inflammatory processes of FOP, which precede ectopic calcifications.

The limitation of this report is a lack of genetic evidence for TSC and FOP. Even though it is more commonly assessable in TSC, the cost of testing for FOP is too high for the parents. The options for FOP management remain limited in the case of either medical or surgical intervention. Imaging features should be evaluated cautiously to avoid unnecessary surgical intervention and biopsy that may worsen the condition.

Conflicts of Interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

References