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ABOUT COVER

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AIMS AND SCOPE

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EDITORIAL

Intersection of two rare conditions: Clinical reflection on tuberous sclerosis combined with primary lymphedema

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Abstract

This editorial discusses a case report recently published in the *World Journal of Clinical Cases*. The report describes the clinical presentation, imaging, diagnosis, and treatment of a patient with tuberous sclerosis complex (TSC) combined with primary lymphedema (PLE). Additionally, it retrospectively analyzes the data of 16 previously reported cases of children with TSC combined with PLE to summarize the epidemiology, genetic diagnosis, and current main treatments of these patients. The report also speculates on the pathological and physiological mechanisms underlying TSC combined with PLE. TSC combined with PLE is rare; therefore, the report provides a theoretical basis for understanding the pathophysiological mechanisms and treatment options for patients with TSC and PLE. Comprehensive clinical management of TSC is essential due to the diverse and multiorgan nature of its manifestations, often requiring a multidisciplinary approach for newly diagnosed cases.

Key Words: Tuberous sclerosis complex; Lymphedema; Examination; Diagnosis; Treatment

Core Tip: Accurate diagnosis of tuberous sclerosis complex (TSC) combined with primary lymphedema (PLE) is challenging due its rarity. Summarizing the clinical and imaging manifestations of TSC-PLE patients, along with molecular genetic studies, offers significant theoretical support for TSC-PLE.

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome that affects multiple organs, including the skin, brain, heart, kidneys, and lungs, caused by defects in the TSC1/TSC2 complex, which inhibits the mammalian target of rapamycin (mTOR) pathway[1]. The incidence of TSC is approximately 1 in 6000 to 1 in 10000, with a mean age of onset of around 7.5 years. TSC primarily affects children[2-4]. In affected children, mutations in the tumor suppressor genes *TSC1* or *TSC2* on chromosome 9q34 and 16p13.3 activate the mTOR pathway, leading to abnormal cell proliferation and the formation of misshapen tumors in multiple organs[5,6].

Given that TSC disrupts the cellular structure of multiple organs, its clinical phenotype is diverse. TSC can cause multisystem damage to the skin, heart, nerves, kidneys and other organs and systems. In children, the disease often begins with epileptic symptoms, and 90% of children experience seizures during their lifetime[7]. The diagnosis of TSC is challenging, as previous diagnostic criteria include multiple characteristic clinical changes, which are difficult to recognize. According to the new diagnostic criteria, genetic detection of a pathogenic mutation in the *TSC1* or *TSC2* genes is significant for the diagnosis of TSC regardless of the presence or absence of clinical manifestations, constituting an independent diagnostic criterion[8]. Treatment primarily focuses on managing symptoms caused by the misshapen tumors and taking preventive measures to avoid loss of function in the affected organs. Traditional treatment of TSC mainly involves surgery and symptomatic support. In recent years, the treatment of TSC has also emphasized the use of molecularly targeted drugs[9]. TSC is a systemic disease; therefore, multidisciplinary follow-up is necessary if multiple organs or tissues are involved. This requires evaluation and follow-up with teams from genetics, neurology, ophthalmology, nephrology, and dentistry, among others.

Lymphedema (LE) is characterized by interstitial edema and protein accumulation due to defective lymphatic drainage. LE can be categorized into two groups: (1) Primary LE (PLE); and (2) Secondary LE. The incidence of PLE is approximately 1 in 10000, with a female to male ratio of 3.5:1. Depending on the age of onset, PLE is classified into three forms: (1) Congenital; (2) Early-onset; and (3) Late-onset[10,11].

Both TSC and PLE are rare diseases, and the probability of their simultaneous occurrence is low. According to current reports, only a dozen cases have been reported internationally. However, there may be correlations between the simultaneous occurrence of these two diseases, providing new ideas for studying the pathogenic mechanism of TSC and PLE.

HIGHLIGHT AND COMMENT

In the May 26th issue of the *World Journal of Clinical Cases*, Li *et al*[12] reported a case of TSC-PLE, retrospectively analyzing the clinical features, imaging, diagnosis and management of a 16-year-old male patient with right lower extremity swelling. The diagnosis of TSC-PLE was successfully confirmed in this patient using advanced imaging methods combined with molecular genetic testing techniques. There are few previous reports on the imaging evaluation of this condition. Therefore, the assessment of the degree of lymphatic dysplasia in this case, along with the collection of imaging evidence for TSC, will contribute to the understanding of TSC-PLE.

It is worth noting that, in some cases, congenital edema is the only external manifestation in children with TSC. The diagnosis of TSC may be particularly difficult in such cases as skin lesions are often difficult to visualize in newborns and, lesions in other tissues are more subtle[13,14]. The initial diagnosis of PLE can be made by ultrasonography and physical examination after birth. The analysis of new cases of TSC-PLE can provide guidance for accurate prenatal diagnosis of fetuses with LE in combination with manifestations of TSC, as well as early diagnosis and tailored therapeutic strategies to improve prognosis. For patients diagnosed with PLE, TSC screening can be routinely performed, such as mTOR immunohistochemistry of pathological tissue biopsies and genetic evaluation of blood samples. Genetic testing of children with congenital LE at birth or even prenatally can help to identify the presence of genetic disorders and thus select treatment options.

With the emergence of precision medicine, the treatment of TSC-PLE is progressively emphasizing molecularly targeted therapies. Targeted therapy with rapamycin, a potent and specific mTOR inhibitor, has been used[15-18]. Rapamycin effectively relieves TSC-related symptoms and can be combined with surgery to reduce the size of lymphatic malformations and stabilize the growth of lymphatic vessels. Among mTOR inhibitors, everolimus is also often a drug of choice. Symptomatic treatments, such as liposuction and volume reduction for LE, can be chosen on the basis of targeted therapy. Antiepileptic drugs are also used in early epileptic episodes to mitigate the damage to growth and development. In this group of children, the use of appropriate medication should be initiated when abnormal epileptic waves appear on the electroencephalography, even in the absence of clinical manifestations[10,15].

Li *et al*[12] reviewed the literature of 16 previously reported cases of TSC-PLE, and found that there may be a gender predisposition for onset. They summarized all the reported cases, and recorded in detail the clinical manifestations of the

patients, the mutated genes, and the corresponding treatments for different cases in a tabular format.

LIMITATION

From the summary of the data, it appears that females with TSC are more frequently affected by LE than male patients; a phenomenon that Li *et al*[12] speculate may be related to estrogen concentration[19]. Patients carrying the *TSC2* causative gene are also more likely to develop LE than those carrying the *TSC1* causative gene. The mechanisms behind these observations are still unclear and need further exploration. Selection bias may also exist due to the small number of cases. Further studies with large numbers of PLE-TSC patients are needed to minimize selection bias.

This study was limited by its retrospective design and small sample size, and the pathophysiological mechanisms leading to the development of LE are currently unknown due to the lack of clinical details and the lack of testing in some patients. It is currently believed that mutations in the *TSC* gene lead to activation of the mTOR pathway, but the specific relationship between mTOR and the formation and growth of lymphatic vessels still needs to be investigated.

Some studies have found that mTOR inhibitors can improve LE in some patients with TSC-PLE, but there is no significant change in the presence of lymphatic vessel malformations[11,20]. In some patients, the size and extent of LE remained unchanged, with no significant improvement or deterioration after drug treatment. Therefore, defining the therapeutic range of mTOR inhibitors such as rapamycin used in the treatment regimen and the systematic assessment of the therapeutic outcome remain areas for further investigation. The conjecture that rapamycin may inhibit lymphangiogenesis by downregulating vascular endothelial growth factor expression in p-mTOR-negative cases also lacks confirmation in prospective randomized trials. Data on the safety, efficacy, and the prognosis of mTOR inhibitors in treating infants and children with TSC-PLE are limited, leading to an inability to predict adverse events with prolonged medication use and long-term safety under maintenance therapy. Further investigation is needed to select early drug treatment measures and evaluate preventive efficacy in children with TSC-PLE.

CONCLUSION

The case report of TSC-PLE enhances clinical understanding of this rare disease and underscores the importance of identifying children with PLE in the context of TSC. While improving the early diagnosis of children, it is important to raise awareness of the various manifestations of this disease. The study of the pathophysiological mechanisms and therapeutic options is essential to improve diagnostic strategies and therapeutic interventions for patients with TSC-PLE. In this context, the need for tailored therapeutic strategies is also emphasized, allowing individualized symptomatic treatment and relief while targeting children with different clinical presentations.

FOOTNOTES

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REFERENCES

1 **Li Y**, Si Z, Zhao W, Xie C, Zhang X, Liu J, Liu J, Xia Z. Tuberous sclerosis complex: a case report and literature review. *Ital J Pediatr* 2023; **49**: 116 [PMID: 37679848 DOI: 10.1186/s13052-023-01490-z]

2 **Shitara N**. [Tuberous sclerosis complex]. *Nihon Rinsho* 2005; **63** Suppl 9: 170-176 [PMID: 16201519]

3 **Grajkowska W**, Kotulska K, Jurkiewicz E, Matyja E. Brain lesions in tuberous sclerosis complex. Review. *Folia Neuropathol* 2010; **48**: 139-

149 [PMID: 20924998]
4 **Grévent D**, Calmon R, Brunelle F, Boddaert N. [Brain imaging in seizures]. *Rev Prat* 2012; **62**: 1391-1394 [PMID: 23424919]
5 **Man A**, Di Scipio M, Grewal S, Suk Y, Trinari E, Ejaz R, Whitney R. The Genetics of Tuberous Sclerosis Complex and Related mTORopathies: Current Understanding and Future Directions. *Genes (Basel)* 2024; **15**: 332 [PMID: 38540392 DOI: 10.3390/genes15030332]
6 **Uysal SP**, Şahin M. Tuberous sclerosis: a review of the past, present, and future. *Turk J Med Sci* 2020; **50**: 1665-1676 [PMID: 32222129 DOI: 10.3906/sag-2002-133]
7 **Nabbout R**, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, Dahlin M, D Amato L, d'Augères GB, de Vries PJ, Ferreira JC, Feucht M, Fladrowski C, Hertzberg C, Jozwiak S, Lawson JA, Macaya A, Marques R, O'Callaghan F, Qin J, Sander V, Sauter M, Shah S, Takahashi Y, Touraine R, Youroukos S, Zonnenberg B, Jansen A, Kingswood JC; TOSCA Consortium and TOSCA Investigators. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA Study. *Epilepsia Open* 2019; **4**: 73-84 [PMID: 30868117 DOI: 10.1002/epi4.12286]
8 **Northrup H**, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, Frost MD, Fuchs Z, Gosnell ES, Gupta N, Jansen AC, Jóźwiak S, Kingswood JC, Knilans TK, McCormack FX, Pounders A, Roberds SL, Rodriguez-Buritica DF, Roth J, Sampson JR, Sparagana S, Thiele EA, Weiner HL, Wheless JW, Towbin AJ, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. *Pediatr Neurol* 2021; **123**: 50-66 [PMID: 34399110 DOI: 10.1016/j.pediatrneurol.2021.07.011]
9 **Pearsson K**, Björk Werner J, Lundgren J, Gränse L, Karlsson E, Källén K, Eklund EA, Bekassy Z. Childhood tuberous sclerosis complex in southern Sweden: a paradigm shift in diagnosis and treatment. *BMC Pediatr* 2023; **23**: 329 [PMID: 37386496 DOI: 10.1186/s12887-023-04137-4]
10 **Klinner J**, Krüger M, Brunet T, Makowski C, Riedhammer KM, Mollweide A, Wagner M, Hoefele J. Congenital lymphedema as a rare and first symptom of tuberous sclerosis complex. *Gene* 2020; **753**: 144815 [PMID: 32479982 DOI: 10.1016/j.gene.2020.144815]
11 **Geffrey AL**, Shinnick JE, Staley BA, Boronat S, Thiele EA. Lymphedema in tuberous sclerosis complex. *Am J Med Genet A* 2014; **164** A: 1438-1442 [PMID: 24668795 DOI: 10.1002/ajmg.a.36469]
12 **Li XP**, Sun XL, Liu X, Wen Z, Jiang LH, Fu Y, Yue YL, Wang RG. Tuberous sclerosis complex combined with primary lymphedema: A case report. *World J Clin Cases* 2024; **12**: 2642-2648 [PMID: 38817219 DOI: 10.12998/wjcc.v12.i15.2642]
13 **Hirsch RJ**, Silverberg NB, Laude T, Weinberg JM. Tuberous sclerosis associated with congenital lymphedema. *Pediatr Dermatol* 1999; **16**: 407-408 [PMID: 10627220 DOI: 10.1046/j.1525-1470.1999.016005406.2.x]
14 **Hoshiai S**, Oguma E, Sato Y, Konishi T, Minami M. Congenital focal lymphedema as a diagnostic clue to tuberous sclerosis complex: report of two cases diagnosed by ultrasound. *Skeletal Radiol* 2015; **44**: 1165-1168 [PMID: 25616615 DOI: 10.1007/s00256-015-2094-8]
15 **Saffari A**, Brösse I, Wiemer-Kruel A, Wilken B, Kreuzaler P, Hahn A, Bernhard MK, van Tilburg CM, Hoffmann GF, Gorenflo M, Hethey S, Kaiser O, Kölker S, Wagner R, Witt O, Merkenschlager A, Möckel A, Roser T, Schlump JU, Serfling A, Spiegler J, Milde T, Ziegler A, Syrbe S. Safety and efficacy of mTOR inhibitor treatment in patients with tuberous sclerosis complex under 2 years of age - a multicenter retrospective study. *Orphanet J Rare Dis* 2019; **14**: 96 [PMID: 31053163 DOI: 10.1186/s13023-019-1077-6]
16 **Huang J**, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. *Biochem J* 2008; **412**: 179-190 [PMID: 18466115 DOI: 10.1042/BJ20080281]
17 **Navarre P**, Poitras B. Lymphoedema in tuberous sclerosis: case report and review of the literature. *J Pediatr Orthop* 2014; **34**: e27-e32 [PMID: 24992349 DOI: 10.1097/BPO.0000000000000240]
18 **Wiemer-Kruel A**, Mayer H, Ewert P, Martinoff S, Eckstein HH, Kriebel T, Bissler J, Franz D, Bast T. Congenital Lymphatic Malformation and Aortic Aneurysm in a Patient with TSC2 Mutation. *Neuropediatrics* 2020; **51**: 57-61 [PMID: 31505689 DOI: 10.1055/s-0039-1694985]
19 **Sukulal K**, Namboodiri N. Congenital lymphedema: another unique and gender specific stigmata of tuberous sclerosis? *Indian Pediatr* 2012; **49**: 845 [PMID: 23144114 DOI: 10.1007/s13312-012-0178-2]
20 **Prato G**, Mancardi MM, Baglietto MG, Janis S, Vercellino N, Rossi A, Consales A, Raso A, Garrè ML. Congenital segmental lymphedema in tuberous sclerosis complex with associated subependymal giant cell astrocytomas treated with Mammalian target of rapamycin inhibitors. *J Child Neurol* 2014; **29**: NP54-NP57 [PMID: 24056156 DOI: 10.1177/0883073813499969]

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