Resolution of multifocal micronodular pneumocyte hyperplasia with everolimus in a patient with tuberous sclerosis complex

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ABSTRACT
A woman with a diagnosis of tuberous sclerosis complex (TSC) presented with TSC2 gene mutation and various manifestations, including epilepsy, renal angiomyolipomas (AML), and pathologically confirmed multifocal micronodular pneumocyte hyperplasia (MMPH). With oral administration of everolimus (mTOR) inhibitor, MMPH and AML were markedly reduced. Further, after starting treatment with everolimus, serum levels of surfactant protein (SP)-A and SP-D, which reflect type II pneumocyte hyperplasia, decreased to the normal range. At the time of writing of this manuscript, 6 years after starting everolimus, MMPH lesions did not relapse and SP-A/D remained the low levels. This is the first case of everolimus efficacy shown for histologically confirmed MMPH in genetically determined TSC patient, with time course of serum SP-A and SP-D.

1. Introduction
Multifocal micronodular pneumocyte hyperplasia (MMPH) is a rare pulmonary hamartoma of the tuberous sclerosis complex (TSC), characterized by multicentric, well-demarcated nodular growth of type II pneumocytes [1,2]. Updated consensus recommendations for TSC suggest a systemic treatment with mammalian target of rapamycin (mTOR) inhibitors in certain cases, which provides an opportunity to treat multiple manifestations of TSC simultaneously [3]. Recently, 2 case reports showed that the lesion presumed to be MMPH, as determined by computed tomography (CT), was reduced in size following treatment with everolimus [4,5]. However, there have been no reports showing the efficacy of everolimus for pathologically proven MMPH with confirmed TSC1/2 mutations. In addition, these two cases did not report the long-term effect of everolimus for MMPH. Further, there have been no reports of serial changes in serum levels of surfactant protein (SP)-A and SP-D, which have been reported as potential biomarkers for MMPH, throughout the treatment period [6]. Herein, we describe a patient with multiple manifestations of TSC, including pathologically confirmed MMPH. We show computed tomography (CT) images of reduction in MMPH size and change in serum levels of SP-A and SP-D, following a total of 6 years after starting treatment with everolimus.

2. Case
An 18-year-old woman, known to have sporadic TSC, was referred to our department because of multiple ground-glass opacities revealed following CT of her chest (Fig. 1A and B). At the age of three years, TSC was diagnosed following an epileptic seizure. The patient had hypomelanotic macules, facial angiofibromas, subependymal nodules, cortical dysplasia, renal angiomyolipoma (AML), and mental retardation. The serum levels of SP-A (185.0 ng/mL) and SP-D (199.1 ng/mL) were elevated, while the serum levels of KL-6 and tumor markers including carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9), and stage specific embryonic antigen-1 (SLE) were within normal range. Pathological findings of a transbronchial lung biopsy from the right middle lobe revealed enlarged cuboidal cells lining the collapsed alveolar septa (Fig. 2). The patient was diagnosed with MMPH, TSC, and TSC2 mutation as NM_000548.5:c.3750C>G p.(Thr1250Ter) was detected by genetic testing. At the age of 20 years, the patient underwent...
trans-arterial embolization for left AML; however, the AML continued to progress. At age 21 years, the epilepsy worsened, and the patient began receiving antiepileptic drugs; however, the epilepsy occurred periodically. On the other hands, Chest CT taken annually showed that MMPH was stable radiographically. At the age of 28 years, given progressing AML (Fig. 1C) and intractable epilepsy, the patient started receiving a mTOR inhibitor, 5 mg/day of everolimus. CT, performed 6 months after starting everolimus, revealed that the lung lesions were less intense than they had been on previous evaluation (Fig. 1D and E). Her serum SP-A and SP-D levels decreased to within the normal range (Table 1). Everolimus also shrunk the AML lesions (Fig. 1F) and facial angiofibroma. In addition, the epileptic seizures with loss of consciousness became less frequently. At the age of 30, 2 years after the start of everolimus, MMPH and AML lesions were kept shrunk (Fig. 1G, H, and I). At the age of 31, the dose of everolimus was increased to 10 mg daily aiming to eliminate epilepsy. However, the patient’s neurological symptoms, pulmonary CT images, renal lesions, and skin lesions did not improved further. The serum levels of SP-A, SP-D, and KL-6 remained within normal range. Two years after the start of everolimus, hemoglobin A1c increased from 5.7% to 6.2%, and the patient required a diet therapy. At the time of writing this manuscript, the patient is 34-year-old and has continued oral everolimus 10 mg daily without her TSC-related symptoms worsened.

3. Discussion

To the best of our knowledge, this is the first report showing the efficacy of everolimus for the treatment of pathologically confirmed MMPH to the patient with genetically confirmed TSC, together with serial changes in serum biomarkers. In addition, this is the first report showing the long-lasting (6 years) effect of everolimus for MMPH.

Following the administration of mTOR inhibitor everolimus, the patient experienced an improvement in several TSC manifestations. It is well known that hamartomas associated with TSC, such as lymphangioleiomyomatosis (LAM), AML, and subependymal giant cell astrocytomas, are caused by mTOR activation with decreased or absent expression of TSC1/2 genes [7,8] and can be treated with mTOR inhibitors [9-11].
4. Conclusion

We present a case of TSC with various clinical manifestations, including MMPH. The patient benefited from treatment with everolimus, with reduced MMPH and a decrease in serum SP-A and SP-D levels.

Disclaimers

None.

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None.

Author contributions

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Declaration of competing interest

All authors inform that there is no conflict of interest.

References

[1] F.M. von Ranke, G. Zanetti, J.L. e Silva, C.A. Araujo Neto, M.C. Godoy, C.A. Souza, A.D. Mancano, A.S. Souza Jr., D.L. Esquisaito, B. Hochhegger, E. Marchiori, Tuberous sclerosis complex: state-of-the-art review with a focus on pulmonary involvement, Lung 193 (5) (2015) 619–627.

[2] T. Hayashi, T. Kamakase, K. Mitani, T. Yao, K. Suda, K. Seyama, Loss of heterozygosity on tuberous sclerosis complex genes in multifocal micronodular pneumocyte hyperplasia, Mod. Pathol. 23 (9) (2010) 1251–1260.

[3] H. Northrup, D.A. Krueger, G. International, Tuberous sclerosis complex consensus, tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference, Pediatr. Neurol. 49 (4) (2013) 243–254.

[4] K.H. Lim, E.J. Silverstone, D.H. Yates, Multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis complex: resolution with everolimus treatment, Am. J. Respir. Crit. Care Med. 201 (10) (2020) e76.

[5] C. Daccord, A. Nicolas, R. Demicheli, H. Chehade, A.F. Hottinger, C. Beigelman, R. Lazzer, Effect of everolimus on multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis complex, Respir Med Case Rep 31 (2020) 101310.

[6] S. Konno, M. Shigemura, T. Ogi, K. Shimizu, M. Suzuki, K. Kaga, Y. Hida, Y. Matsuno, M. Nishimura, Clinical course of histologically proven multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis complex: a case series and comparison with lymphangiomyomatosis, Respiration 95 (5) (2018) 310–316.

[7] Y. Niida, A.O. Stemmer-Rachamimov, M. Logrip, D. Tapon, P. Perez, D. J. Kwiatkowski, K. Sims, M. MacCollin, D.N. Louis, V. Ramesh, Survey of somatic mutations in tuberous sclerosis complex (TSC) hamartomas suggests different genetic mechanisms for pathogenesis of TSC lesions, Am. J. Hum. Genet. 69 (3) (2001) 493–503.

[8] P. Curatolo, R. Bombardieri, S. Jozwiak, Tuberous sclerosis, Lancet 372 (2008) 657–668.

[9] J.J. Bissler, J.C. Kingswood, E. Radzikowska, B.A. Zonenberg, M. Frost, E. Belousova, M. Sauter, N. Nonomura, S. Brakemeier, P.J. de Vries, V. H. Whittemore, D. Chen, T. Sahmoud, G. Shah, J. Lincy, D. Lebowih, K. Buddle, Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial, Lancet 381 (9869) (2013) 817–824.

[10] Q. Wang, M. Luo, B. Xiang, S. Chen, Y. Ji, The efficacy and safety of pharmacological treatments for lymphangiomyomatosis, Respir. Res. 21 (1) (2020) 55.

[11] D.N. Franz, E. Belousova, S. Spargana, E.M. Bebin, M. Frost, R. Kuperman, O. Witt, M.H. Kohrn, J.R. Flaminii, J.Y. Wu, P. Curatolo, P.J. de Vries, V. H. Whittemore, E.A. Etchel, P.R. Ford, G. Shah, H. Cauvel, D. Lebowih, T. Sahmoud, S. Jozwiak, Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial, Lancet 381 (9861) (2013) 125–132.

[12] T. Shoji, S. Konno, Y. Niida, T. Ogi, M. Suzuki, K. Shimizu, Y. Hida, K. Kaga, K. Seyama, T. Naka, Y. Matsuno, M. Nishimura, Familial multifocal micronodular pneumocyte hyperplasia with a novel splicing mutation in TSC1: three cases in one family, PLoS One 14 (2) (2019), e0221370.

[13] J.A. French, J.A. Lawson, Z. Yapici, H. Ikeda, T. Polster, R. Nabbout, P. Curatolo, P.J. de Vries, D.J. Dlugos, N. Berkowitz, M. Voi, S. Peyrard, D. Pelov, D.N. Franz, Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study, Lancet 388 (10056) (2016) 2153–2163.

[14] N. Ishikawa, N. Hattori, A. Yokoyama, N. Koorno, Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases, Respir Investig 50 (1) (2012) 9–13.

[15] S.R. Walker, M.C. Williams, B. Benson, Immunocytotoxic chemical localization of the major surfactant apoproteins in type ii alveolar, Clara cells, and alveolar macrophages of rat lung, J. Histochem. Cytochem. 34 (9) (1986) 1137–1148.

[16] W.F. Voorhout, T. Veenendaal, Y. Kuroki, Y. Ogasawara, L.M. van Golde, H. J. Geuze, Immunocytotoxic chemical localization of surfactant protein D (SP-D) in type ii alveolar cells, Clara cells, and alveolar macrophages of rat lung, J. Histochem. Cytochem. 40 (10) (1992) 1589–1597.

[17] H. Takahashi, T. Fujishima, H. Kobayashi, T. Shiratori, Y. Kuroki, S. Abe, Serum surfactant proteins A and D as prognostic factors in idiopathic pulmonary fibrosis and their relationship to disease extent, Am. J. Respir. Crit. Care Med. 162 (3) (2000) 1109–1114.

[18] N. Kocono, T. Awaysa, T. Oyama, M. Yamakido, M. Akuyama, Y. Inoue, A. Yokoyama, H. Hamada, S. Fujioka, K. Hiwada, KL-6, a mucin-like glycoprotein,
in bronchoalveolar lavage fluid from patients with interstitial lung disease, Am. Rev. Respir. Dis. 148 (3) (1993) 637–642.

[19] Y. Hosokawa, Y. Tsuchihashi, K. Ochiai, R. Hino, M. Kuga, T. Ashihara, An autopsy case of tuberous sclerosis with multiple hamartomatosis (in Japanese), Risho Byori 8 (1990) 389–396.

[20] A. Cancellieri, V. Poletti, B. Corrin, Respiratory failure due to micronodular type II pneumocyte hyperplasia, Histopathology 41 (3) (2002) 263–265.