Respiratory Medicine Case Reports 34 (2021) 101526

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

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

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ARTICLE INFO

*Keywords:*
Tuberous sclerosis complex
Multifocal micronodular pneumocyte hyperplasia
Everolimus
Surfactant Protein-A (SP-A)
Surfactant protein-B (SP–B)

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, a mammalian target of rapamycin (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 out 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 (SLX) 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

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https://doi.org/10.1016/j.rmcr.2021.101526
Received 3 August 2021; Received in revised form 20 September 2021; Accepted 4 October 2021
Available online 6 October 2021

*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 A 1c 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.

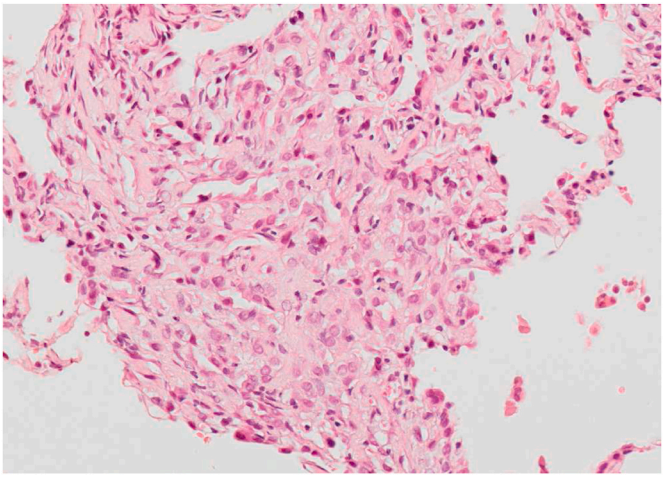

**Fig. 2.** The histological findings of transbronchial lung biopsy representing multifocal micronodular pneumocyte hyperplasia (hematoxylin and eosin staining, original maginification × 20). A demarcated nodular lesion comprised of alveolar lining of enlarged cuboidal cells. These cells have abundant pale to eosinophilic cytoplasms and round to oval-shaped nuclei, reminiscent of type II pneumocyte proliferation.

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].

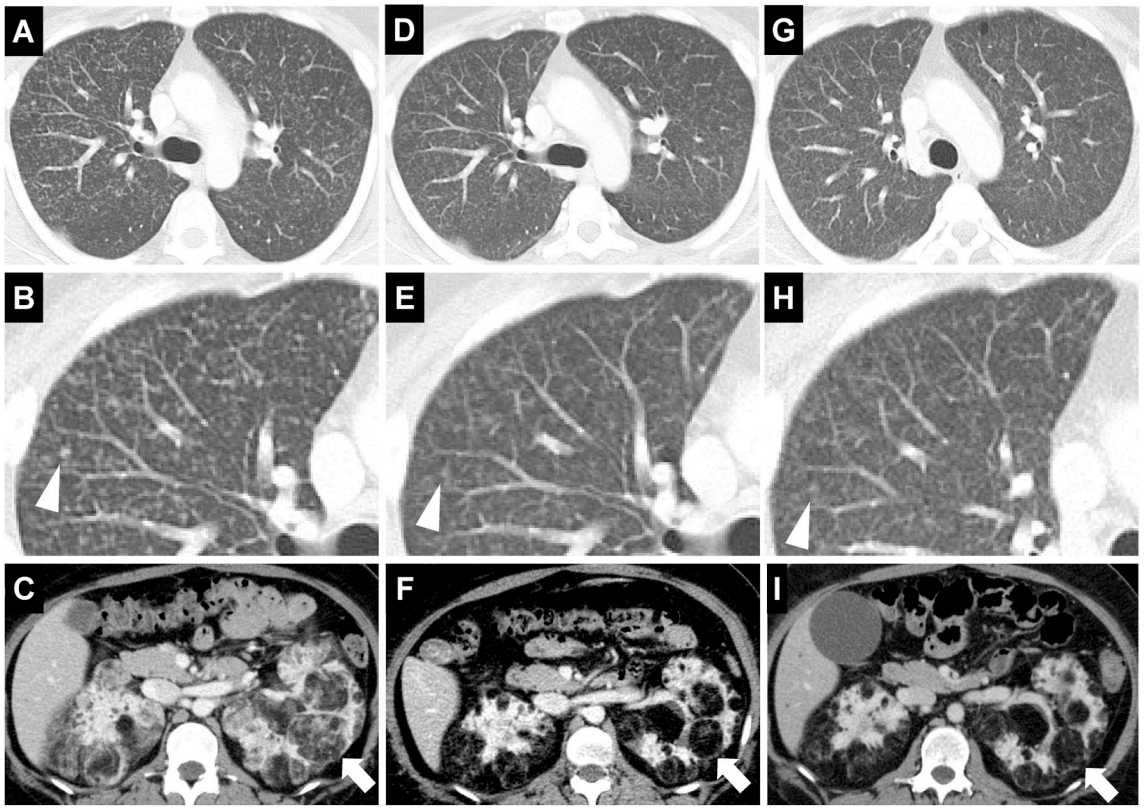


**Fig. 1.** Computed tomography images of multifocal micronodular pneumocyte hyperplasia (MMPH) and renal angiomyolipoma (AML). (A) (B) MMPH images at the age of 18 and before initiation of treatment with everolimus. (C) AML image at the age of 28 and before initiation of everolimus. (D) (E) MMPH and (F) AML at the age of 28, 6 months after initiation of treatment with everolimus. (G) (H) MMPH and (I) AML at the age of 30, 2 years after initiation of treatment with everolimus. Representative lesions were shown with arrow heads (MMPH) and arrows (AML).

**Table 1**
The serum levels of SP-A, SP-D, and KL-6 in the patient.

| Age (years) | 25 | 26 | 29 | 30 | 31 |
|---|---|---|---|---|---|
| SP-A (ng/mL) | 185.0 | 152.0 | 48.0 | 51.7 | 42.3 |
| SP-D (ng/mL) | 199.1 | 188.1 | 84.2 | 52.6 | 69.8 |
| KL-6 (U/mL) | 322 | 284 | 302 | 307 | 305 |

SP-A and SP-D levels decreased after daily treatment with 5 mg of everolimus was introduced at the age of 28 years. Abbreviation: SP-A (Surfactant protein-A); SP-D (Surfactant protein-D); KL-6 (Krebs von den Lungen-6). Normal range: SP-A 0.0–43.7 (ng/mL); SP-D 0.0–109.9 (ng/mL); KL-6 105.3–401.2 (U/mL).

Loss of heterozygosity for TSC1/2 genes and high expression of phospho-p70S6K and phospho-4E-BP1 proteins observed in MMPH lesions suggest the activation of mTOR pathway and plausibility of a response to mTOR inhibitors [2,12]. In addition, mTOR inhibitors improve seizures in TSC, as observed in this case [13].

Serial changes in several important serum biomarkers are of significant interest in this case. Krebs von den lungen-6 (KL-6), SP-A, and SP-D are unique biomarkers associated with interstitial lung diseases [14–16]. We previously reported that the serum levels of SP-A and SP-D were elevated whereas KL-6 was within normal range in MMPH patients and that MMPH lesions were stable radiographically [6]. In the present case, we also noted the different patterns of serum KL-6 and SP-A/SP-D associated with the clinical course of this case. Serum levels of SP-A/SP-D returned to normal in response to everolimus. However, this was not the case for serum level of KL-6. Among the possible explanations for this dissociation, previous reports have focused on the functional differences between these proteins. SP-A and SP-D are both secretory proteins and are associated with the extent of cell proliferation and alveolitis [17]. KL-6 serves as a structural component of the cell membrane and increased serum levels of KL-6 might be related to structural alveolar destruction and/or extracellular domain cleavage by proteinase for the soluble form to increase [18]. Discordant serum level of these biomarkers might indicate that MMPH is characterized by type II alveolar cell proliferation rather than alveolar cell damage.

We recently reported the clinical course of nine cases of MMPH diagnosis in our department [6]. No cases exhibited deterioration of pulmonary function during the follow-up period (4–13 years). In contrast, previous reports described some cases with chronic dyspnea, cough, mild hypoxemia, and rarely, respiratory compromise, possibly due to worsening of MMPH [19,20]. Although the patient mentioned in this report did not have respiratory symptoms or reduced pulmonary functions related to MMPH, this case provided evidence that everolimus is a potential candidate for the treatment of MMPH when lesions and respiratory symptoms worsen.

## 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.

## Sources of support

None.

## Author contributions

Conceptualization: Tetsuaki Shoji, Satoshi Konno.
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Writing – original draft: Tetsuaki Shoji.
Writing – review & editing: Satoshi Konno.

## Declaration of competing interest

All authors inform that there is no conflict of interest.

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