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Case report

Effect of everolimus on multifocal micronodular pneumocyte hyperplasia in tuberous sclerosis complex

Cécile Daccord [a,*], Aymeric Nicolas [b], Rita Demicheli [c], Hassib Chehade [d], Andreas F. Hottinger [c,e], Catherine Beigelman [b], Romain Lazor [a]

[a] Department of Respiratory Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[b] Department of Radiodiagnostic and Interventional Radiology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[c] Department of Oncology, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[d] Department Woman-Mother-Child, Division of Paediatrics, Paediatric Nephrology Unit, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland
[e] Department of Clinical Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne, Switzerland

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ABSTRACT

Multifocal micronodular pneumocyte hyperplasia (MMPH) is a benign proliferation of alveolar type II cells presenting as multiple pulmonary nodules at chest imaging, which is frequently seen in patients with tuberous sclerosis complex (TSC). We report a case of a woman with TSC and MMPH who received everolimus, a mechanistic target of rapamycin (mTOR) inhibitor, for the treatment of a subependymal giant cell astrocytoma (SEGA). After 3 months of therapy, a remarkable decrease in density of all pulmonary MMPH lesions was observed, without any change in size. This shows that everolimus is active on MMPH similarly to its effects on SEGA, renal angiomyolipomas, and pulmonary lymphangioleiomyomatosis in TSC, and suggests that the dysregulated activation of mTOR which characterizes TSC also plays a role in the pathogenesis of MMPH.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder caused by inactivating mutations in the tumor suppressor genes *TSC1* or *TSC2* coding for hamartin and tuberin [1]. These proteins form an intracellular complex that inhibits the mechanistic target of rapamycin (mTOR), a key regulator of cell growth and proliferation. In TSC, the loss of hamartin or tuberin leads to constitutive activation of mTOR and abnormal cell growth and proliferation, resulting in development of hamartomas in various organs such as subependymal giant cell astrocytomas (SEGAs) and renal angiomyolipomas (AMLs) [1]. Pulmonary manifestations of TSC include lymphangioleiomyomatosis (LAM), a rare condition characterized by cystic destruction of lung parenchyma, and multifocal micronodular pneumocyte hyperplasia (MMPH), a benign proliferation of alveolar type II cells presenting as multiple pulmonary nodules scattered throughout the lungs.

Pharmacological inhibition of mTOR with sirolimus and everolimus leads to decrease in size of SEGAs and renal AMLs in TSC [2,3], and stabilizes lung function in LAM [4], but its effect on MMPH is unclear.

2. Case report

A 20-year old woman was diagnosed at birth as having TSC. She developed epilepsy at the age of 15 months. Brain magnetic resonance imaging (MRI) revealed a SEGA and cortical tubers. Other typical manifestations that appeared progressively over time included multiple renal AMLs, cardiac rhabdomyoma, facial angiofibromas, hypomelanotic macules and ungueal fibromas. No genetic testing was performed in the patient, but genetic analysis in both parents did not detect any *TSC1* or *TSC2* mutation.

At the age of 14, the gradual growth of the SEGA led to hydrocephalus, which was treated by ventriculoperitoneal shunting and fenestration of the septum pellucidum. Due to recurrent intracranial hypertension, incomplete surgical removal of the tumor was performed 3 months later, and the diagnosis of SEGA was confirmed at histopathology.

At the age of 15, a growing right renal mass suspect of AML led to selective arterial renal embolization and concomitant needle biopsy. Despite careful histopathological examination and external review, it was not possible to discriminate between epithelioid AML and papillary

* Corresponding author. Service de Pneumologie, Centre hospitalier universitaire vaudois (CHUV) BU44.07.2108, Rue du Bugnon 44, 1011, Lausanne, Switzerland.
E-mail address: cecile.daccord@chuv.ch (C. Daccord).

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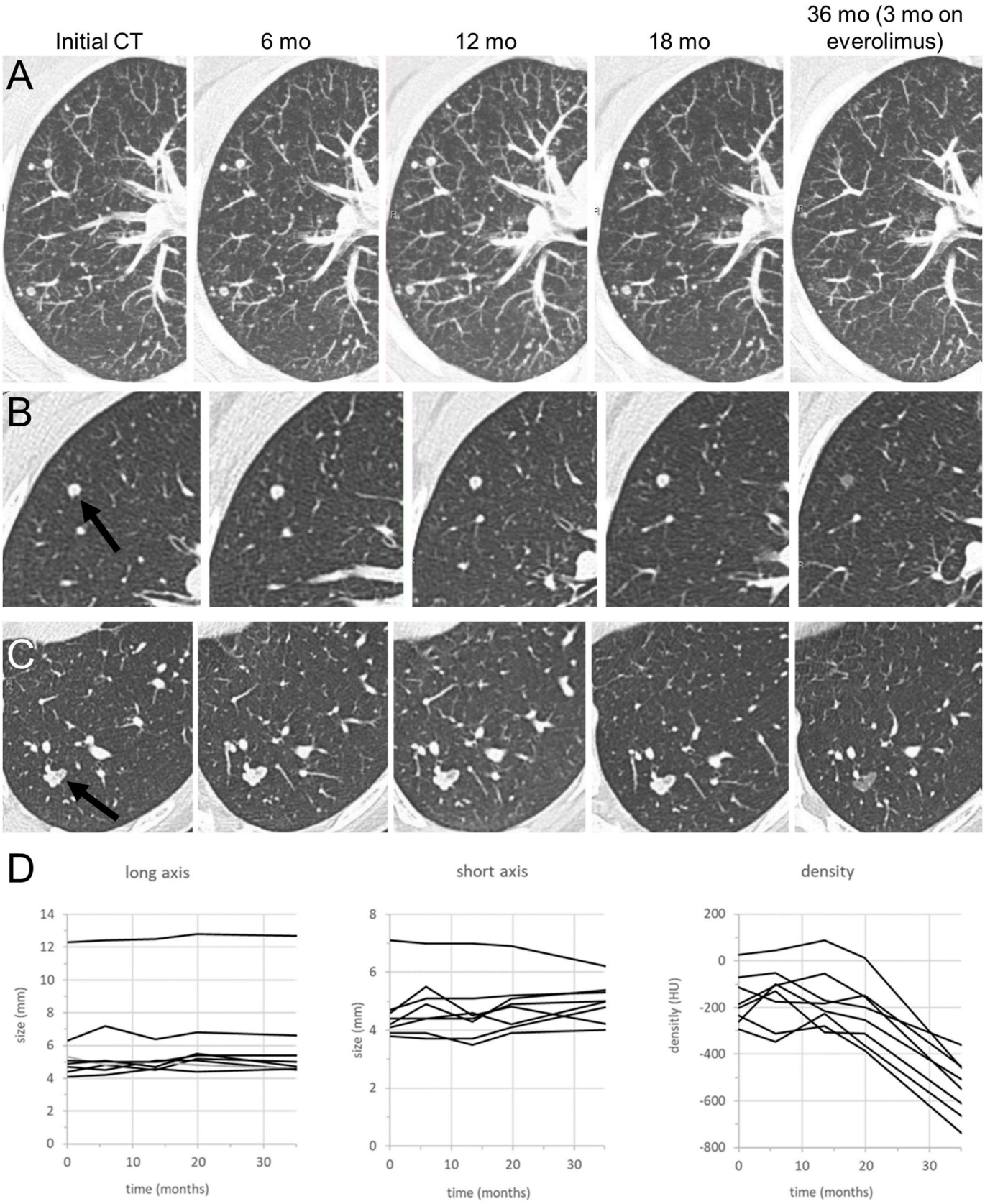

Fig. 1. Chest HRCT at 0, 6, 12, 18 and 36 months (mo): stability in size, shape and density of numerous small pulmonary nodules with a random distribution on the 4 first HRCTs, followed by a significant decrease in density of all pulmonary nodules at 36 months, i.e. 3 months after everolimus initiation (A). Similar observation focused on selected nodules in the right upper lobe (B) and left lower lobe (C). Follow-up of dimensions (long and short axis) in millimeters (mm) and density using Hounsfield Unit (HU) values of the 8 most easily perceptible solid nodules, showing no change in size over time before (first 4 HRCTs) and after (last HRCT) everolimus initiation, but a decrease in density on the last HRCT performed 3 months after treatment onset (D).

renal cell carcinoma, and regular imaging follow-up was instituted. A chest high-resolution CT (HRCT) revealed numerous small pulmonary nodules randomly distributed throughout both lungs.

At first visit to our Department, the patient was a non-smoker and had no respiratory symptoms. Lung auscultation was unremarkable. Pulmonary function tests showed normal lung volumes and carbon monoxide transfer coefficient. There was no feature suggesting an infection, including tuberculosis. In the absence of cystic lung lesions on HRCT, LAM was ruled out. Follow-up HRCT at 6, 12 and 18 months showed stability in the number, size and density of all pulmonary nodules, thus reducing the likelihood of metastatic disease and suggesting MMPH. Moreover, the renal mass remained stable for 2 years after embolization, thus reinforcing the hypothesis of AML.

At the age of 18, owing to progressive SEGA growth and increased seizure frequency, the patient was started on everolimus 10 mg daily. The treatment was well tolerated. Brain MRI after 3 months showed a significant reduction in SEGA size, which subsequently remained stable at 8 and 11 months of treatment. A follow-up chest HRCT performed 3 months after everolimus initiation (and 3 years after the first thoracic imaging) showed a remarkable decrease in density of all pulmonary MMPH lesions, without obvious change in size (Fig. 1A–C). We measured the diameter and density of the 8 most easily perceptible solid nodules on the 4 HRCT performed before everolimus, and the last one on everolimus. As shown in Fig. 1D, long and short axis (axial view) of all 8 nodules did not change over time either before or after everolimus therapy. In contrast, the density of all 8 nodules decreased after everolimus initiation, suggesting a therapeutic effect of everolimus on these lesions. Abdominal HRCT at 3 months of treatment also demonstrated a decreased density of all AMLs.

3. Discussion

MMPH was first described in 1991 on open-lung biopsy in a 38-year old female with TSC [5]. Except for rare sporadic cases [6,7], MMPH seems systematically associated with TSC, with or without concomitant LAM. Unlike LAM, which predominantly affects women, MMPH has no gender predilection [8,9]. Its exact prevalence is unknown, but pulmonary changes consistent with MMPH have been found on chest imaging in >50% of patients with TSC in large series [8–10].

Classical imaging features of MMPH include multiple well-delimited solid nodules or poorly defined nodular ground glass opacities, often with areas of increased density corresponding to papillary growth pattern of type II pneumocytes [8,11,12]. Target-appearing lesions corresponding to ground-glass nodules with increased density in the periphery have also been reported [8]. The lesions typically range from 1 to 10 mm in diameter and are diffusely scattered throughout the lungs in a random distribution, and less commonly with upper lobe or peripheral predominance [8,11,12].

Histologically, MMPH consists of well-delimited multicentric areas of hyperplasia and proliferation of benign type II pneumocytes lining the alveolar septa, with preserved alveolar architecture and an associated increase in alveolar macrophages, together with adjacent mild fibrotic interstitial thickening and lymphocytic infiltrates [6]. MMPH lesions exhibit positive staining for cytokeratin, epithelial membrane antigen and surfactant proteins, which supports their epithelial origin. Negative staining for monoclonal antibody HMB-45 and actin confirms that MMPH is distinct from LAM [6,12].

MMPH is usually asymptomatic, does not impact lung function, and does not significantly progress over time [8,12–14]. It also does not seem to undergo malignant transformation [6]. Therefore, with the exception of one reported case of progressive MMPH in TSC [15], the condition does not appear to be clinically relevant in most patients.

A definite diagnosis of MMPH cannot be made by imaging alone, but a history of TSC, the multifocal and random distribution of lesions, their stability in size and number over time, and the absence of associated respiratory or systemic symptoms are important clues suggesting a diagnosis of MMPH. Lung biopsy is usually not performed except for atypical radiological findings, or nodules progressing in size or number. Given the clinical context, and despite the absence of histological confirmation, we considered MMPH as the most likely diagnosis in the present case.

To our knowledge, this is the second ever observation of a therapeutic effect of mTOR inhibitors on MMPH. Indeed, a recent brief case report of a 25-year old man with TSC also showed a marked reduction of MMPH lesions one year after the introduction of everolimus for AMLs [16]. We speculate that everolimus exerts an anti-synthetic, anti-proliferative and pro-apoptotic effect on MMPH lesions similarly to its effects on SEGA, renal AMLs, and LAM cells. Why did everolimus reduced only nodule density but not nodule size in our case is currently unclear. Longer follow-up could provide more information on this issue.

4. Conclusion

This case report demonstrates that the constitutive activation of mTOR, which characterizes TSC, is also involved in the pathogenesis of MMPH, and that pharmacological inhibition of mTOR could be beneficial in this condition.

Statement of ethics

Written informed consent was obtained from the patient.

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Author contributions

Data collection: CD, AN, RD, HC, AFH. Data analysis: CD, AN, CB, RL. Data interpretation: CD, RL. Manuscript drafting: CD, AN, RL. Critical manuscript revision: all authors. Final manuscript approval: all authors. Holding responsibility for scientific content: RL.

Declaration of competing interest

The authors have no conflicts of interest to declare related to this work. AN, RD and HC have nothing to disclose. CD reports non-financial support from Boehringer-Ingelheim and Roche, outside the submitted work. AFH reports grants from Novocure, personal fees from Karyopharm and BMS, outside the submitted work. CB reports personal fees from Boehringer-Ingelheim, AstraZeneca, and Gilead Sciences, outside the submitted work. RL reports personal fees and non-financial support from Boehringer-Ingelheim, non-financial support from Roche and Vifor, outside the submitted work.

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