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Lymphangioleiomyomatosis associated with prolactinoma: A case report and literature review

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ABSTRACT

The thirty-five-year-old woman had been experiencing dyspnea on exertion since her second child's birth five years before presenting to hospital A, where she was diagnosed with lymphangioleiomyomatosis (LAM) based on video-assisted thoracoscopic surgery lung biopsy and referred to our hospital. She was treated with sirolimus for one year. Although her subjective symptom of dyspnea improved, she found that her amenorrhea had persisted for six years. A blood test revealed high prolactin (PRL) levels of 98 ng/mL and head magnetic resonance imaging revealed a pituitary adenoma, which was complicated by a prolactinoma. We continued with follow-up observation without any pharmacotherapy for the prolactinoma. However, she was administered oral cabergoline (0.25 mg per week) when her PRL levels were elevated to 250 ng/mL 38 months after therapeutic intervention with sirolimus. For the next 14 months, her respiratory function and PRL concentration both demonstrated improvement and her condition did not worsen any further. It has been reported that prolactin may exacerbate LAM. Our case suggests that a clinical reduction in PRL levels may also improve LAM.

1. Introduction

Lymphangioleiomyomatosis (LAM) is a rare metastasizing neoplasm that predominantly affects women of childbearing age [1]. It may occur sporadically or in association with the tuberous sclerosis complex (TSC) [2]. The prevalence of LAM is estimated to be 3.4–7.8 per million worldwide and 1.2–2.3 per million in Japan [3]. The 10-year survival rate for LAM is estimated to be over 90%, but its clinical course is variable and some patients may develop respiratory failure [4,5].

Prolactinoma is a semi-autonomous prolactin (PRL)-producing pituitary tumor that accounts for approximately 30% of pituitary tumors and is the most common hormone-producing tumor. The prevalence of prolactinomas in adults is estimated to be 60–100 per million [6,7]. It is most common in women with a male to female ratio of 1:3.6: 90% of cases occur in women of childbearing age, i.e., 20–30 years.

The complications of these two conditions are extremely rare, and to the best of our knowledge, only two other cases have been reported. Some previously reported studies suggested that PRL may play an important role in the progression of LAM, and our case may be the first to provide evidence for the same.

Herein, we described a case of lymphangioleiomyomatosis (LAM) associated with prolactinoma in a woman in the third decade of life.

1.1. Case presentation

A 35-year-old woman visited another hospital for dyspnea on exertion that lasted for 5 years after the birth of her second child. Chest computed tomography (CT) revealed diffusely distributed multiple cysts in both lungs (Fig. 1). She underwent surgical lung biopsy of the left lower lung lobe (S8) at the previous hospital, and was diagnosed with LAM. Thereafter, she was referred to our department for the treatment of LAM, where she was administered sirolimus (1 mg per day). The patient's hypoxemia on exertion disappeared 12 months after the initiation of sirolimus therapy, and the percentage of the predicted forced expiratory volume in 1 s (FEV1%) improved. At that time, the patient informed us that her menstrual cycle had stopped since the birth of her second child. A blood test revealed high serum prolactin (PRL) levels (74.97 ng/mL; normal, 0–40 ng/mL), and brain magnetic resonance imaging revealed a pituitary adenoma measuring 4× 2 mm (Fig. 2).

The patient was asymptomatic and initially refused treatment. Thus, we decided to observe her without treatment. Thereafter, her serum PRL level gradually increased to 252 ng/mL over the next 3 years, although

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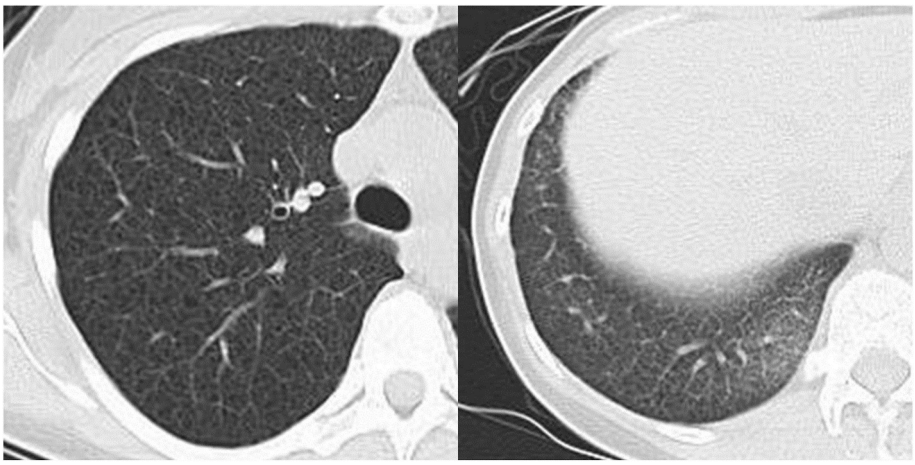

Fig. 1. Chest computed tomography illustrates diffusely distributed multiple cysts in both lungs, which is among the characteristic features of LAM.

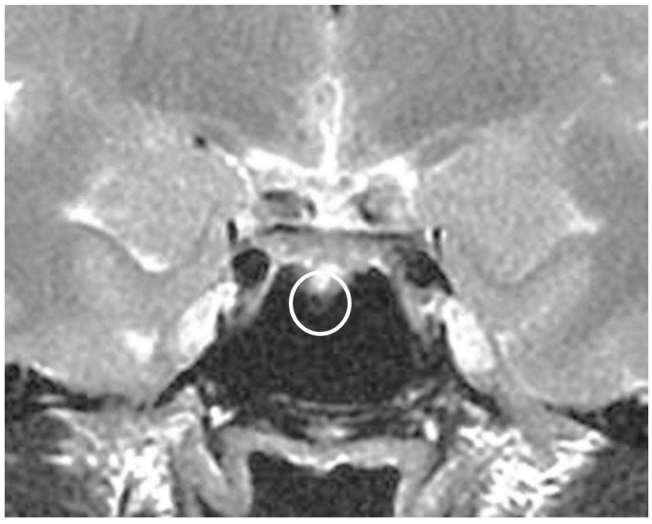

Fig. 2. Brain MRI shows a pituitary adenoma measuring 4 × 2 mm. The persistence of amenorrhea and high PRL levels in blood lead to a diagnosis of prolactinoma. MRI: magnetic resonance imaging.

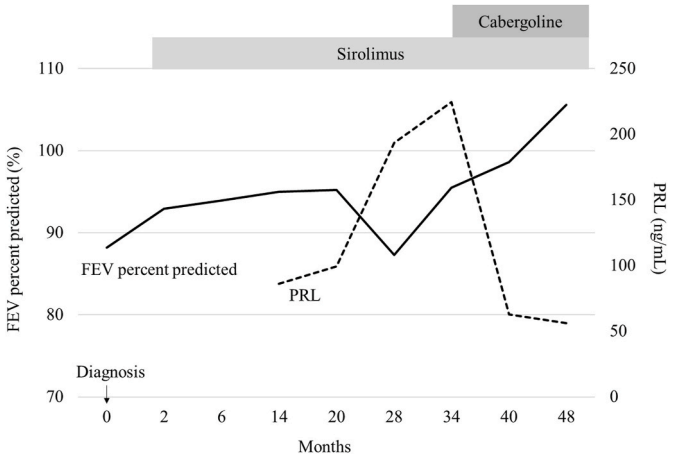

Fig. 3. Time course of the percent predicted forced expiratory volume in 1 s (FEV1%) and prolactin levels.

the size of the pituitary adenoma remained unchanged. At this point, she was still asymptomatic, but her PRL levels promptly dropped to 56.25 ng/mL following the initiation of treatment with cabergoline to reduce the future risk of osteoporosis. The FEV1% rose from 95% to 106% (Fig. 3) during cabergoline therapy. The respiratory symptoms remained the same.

2. Discussion

The hormone PRL suppresses the secretion of estrogen and promotes that of progesterone [8]. LAM is known to be exacerbated by estrogen. However, the question remains that if the treatment for prolactinoma eventually promotes estrogen secretion, would it not eventually exacerbate LAM?

We would like to describe the basic characteristics of LAM before considering the answer to this question. LAM is prevalent in young women and women receiving estrogen replacement therapy. LAM is also found in about 40% of patients with TSC [1]. The typical clinical course of the disease often includes respiratory symptoms such as clinical dyspnea and pneumothorax. The investigative examinations include respiratory function tests, CT, and biopsy. Respiratory function tests show obstructive disturbances and a decrease in the diffusion capacity. Thoracic CT is characterized by diffusely scattered thin-walled cysts. Biopsy is performed in the absence of any salient CT findings and is characterized by the presence of smooth muscle-like cell growth. The molecular pathogenesis of LAM is the second point of consideration. The mTOR pathway is known to be involved in LAM growth. TSC proteins suppress mTOR, and TSC mutations are known to occur in patients with LAM, which increase the likelihood of mTOR activation. Therefore, although various treatments are available for LAM, mTOR inhibitors are the treatment of choice for this condition [9].

The relationship between LAM and PRL is the third point of consideration. Studies have found that LAM cells also contribute to the increased expression of PRL receptors [10]. Hence, patients with LAM are more susceptible to mTOR activation by PRLs. Therefore, mTOR is likely to be activated in patients with LAM for two reasons. First, TSC mutations activate mTOR. Second, the increased sensitivity to PRL is likely to induce mTOR activation. We observed an improvement in the FEV1% along with a decrease in PRL levels after the administration of cabergoline in our patient. Cabergoline administration is thought to have decreased PRL and increased estrogen levels. However, we hypothesized that mechanism of action of cabergoline, i.e., the suppression of LAM cell proliferation resulted from the summation of mTOR activation due to elevated estrogen and mTOR suppression due to decreased PRL. Moreover, it is possible that prolactin lowering was more effective than estrogen activation because the PRL was in the high 200-μL range s

Table 1
Literature review including our case.

References	Sex	Age	Treatment for prolactinoma	Clinical course of LAM
Wilson AM et al. 2001 [11]	Female	43	No	Deteriorated
Hamaguchi R et al. 2012 [12]	Female	42	No	Unchanged
Our case	Female	35	Cabergoline	Improve

in the present case.

To the best of our knowledge, there have been two previous reports of LAM associated with prolactinoma (Table 1) [11,12]. However, the previous two patients had been treated for prolactinoma prior to the diagnosis of LAM and did not undergo simultaneous treatment for hyperprolactinemia and LAM after the diagnosis of LAM. The cause and duration of hyperprolactinemia were unknown in the first patient, who improved with cabergoline administration, and was diagnosed with LAM seven years later. Cabergoline seems to have been discontinued due to menorrhagia. At the time of diagnosis of LAM, the PRL was within the normal range, and the symptoms of LAM subsequently worsened.

The second reported patient had been treated with terguride for 6 years, which was discontinued when she became pregnant, and the diagnosis of LAM was made 7 years later. Although hyperprolactinemia was present at the time of diagnosis of LAM, the patient was only followed-up since there was no exacerbation of symptoms. Thus, our case is extremely important because it suggests that the treatment of hyperprolactinemia along with the treatment of LAM may not lead to worsening of LAM.

3. Conclusion

This case report is important in the following two points. The first is a very rare case of co-morbidity with LAM and prolactinoma. Second, cabergoline treatment for prolactinoma did not exacerbate LAM. The effects of prolactin on the development of LAM are unclear, but cabergoline treatment may be safe in similar cases.

Informed consent

Informed consent was obtained from the patient and family discussed in the report.

Declaration of competing interest

All the authors have no conflict of interest about this case report.

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