Annals of Clinical Case Reports

Case Report
Published: 30 Mar, 2020

Multiple Pulmonary Fibroleiomyomatous Hamartoma

Jiří Škach[1], Peter Hromádka[1], Petr Plaček[2] and Tomáš Zajíc[3]*

[1]Department of Surgery, Regional Hospital Liberec, Czechia

[2]Department of Pneumology, Regional Hospital Liberec, Czechia

[3]Department of Microbiology, Regional Hospital Liberec, Czechia

Abstract

Introduction: Multiple Pulmonary Fibroleimyomatous Hamartoma (MPFH) is a rare disease which occurs mainly in women of middle age and older but also men and children can be affected. Surprisingly, as a rule the diagnosis is not definitely confirmed until histological examination. Due to an indolent nature of hamartomas they are always in practice a coincidental finding. Tumors occur without lung lobe predominance. Their size ranges from small up to several centimeter tumors and they are in the amount of from several to hundreds of nodules in one patient.

Case Presentation: A 72-year-old patient underwent chest X-ray during preoperative examination before arthroscopy. Eight spherical shadows of a metastatic nature were observed in the clinical image. Thoracoscopic resection showed a surprising MPFH finding and regular CT controls were decided on. After eight months there was even a spontaneous regression of one of the tumors.

Discussion: Surgical performance of MPFH is generally indicated after a coincidental chest X-ray finding followed by verified non-specific depiction of metastatic affection on CT. Magnetic resonance and PET do not provide further crucial information. During PET examination tumors are without activity and not even a possible primary tumor is identifiable. If hormonal dependency is confirmed, anti-estrogen therapy should be started or gynecological resection considered.

Conclusion: It is recommended to obtain a representative MPFH sample via thoracoscopy as the results of transparietal biopsy usually are not absolute proof (false negativity). If a patient does not have other problems, the size of tumors and their amount do not progress with the passing of time and at the same time hormonal dependency is not confirmed, regular dispensary care by a pneumologist is sufficient. An alternative treatment is repeated re-resection.

Keywords: Hamartoma; Leiomyoma; Metastasis

OPEN ACCESS

Correspondence:

Jiří Škach, Department of Surgery, Regional Hospital Liberec, Na Vysluni 980, Liberec 14, 46014, Czechia; E-mail: jiri.skach@nemlib.cz

Received Date: *06 Mar 2020*

Accepted Date: *24 Mar 2020*

Published Date: *28 Mar 2020*

Citation:

Škach J, Hromádka P, Plaček P, Zajíc T. Multiple Pulmonary Fibroleiomyomatous Hamartoma. Ann Clin Case Rep. 2020; 5: 1813.

ISSN: 2474-1655

Introduction

Multiple Pulmonary Fibroleimyomatous Hamartoma (MPFH) is a diagnosis first described in literature by Logan [1]. They are slow growing spherical lesions based on a few available case reports of long-term monitored patients [2,3]. From the histological point they are a mixture of smooth muscle tissue and glandular elements which are sharply bordered and they do not have connection either with the bronchial tree or vascular structures of the lung. MPFH diagnosis is typical for women of middle age. Due to their indolent nature they are always in practice a coincidental finding. Tumors occur without lung lobe predominance. Their size ranges from small up to several centimeter tumors and they are in the amount of from several to hundreds of nodules in one patient [4-6]. For a long time, a controversial theory was valid that two clinical-pathological units, Benign Metastasizing Leiomyoma (BML) and Multiple Pulmonary Fibroleimyomatous Hamartoma (MPFH) were identical [7-10]. A number of facts give evidence against this theory. Quite a few case reports in women patients were described where they had not undergone hysterectomy and ovarian leiomyoma had not been diagnosed during long-term monitoring [13]. Furthermore, MPFH case reports in men and also in children were described [11-13]. The potential occurrence of leiomyoma in any unexamined organs (for example a digestive tract) is a question.

Case Presentation

A 72-year-old patient underwent chest X-ray during preoperative examination before arthroscopy. A few spherical shadows (coin lesions) of a metastatic nature and hiatal hernia were observed in the clinical image (Figure 1). The patient did not have any troubles, was without dyspnoea, pains, weight loss, temperature or cough.

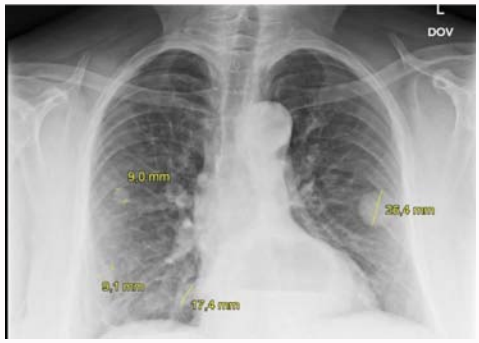

Figure 1: Chest X-ray image.

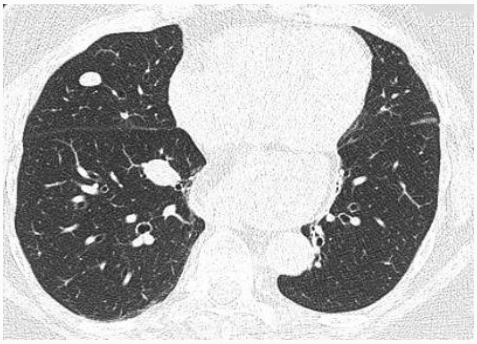

Figure 2: CT scan images.

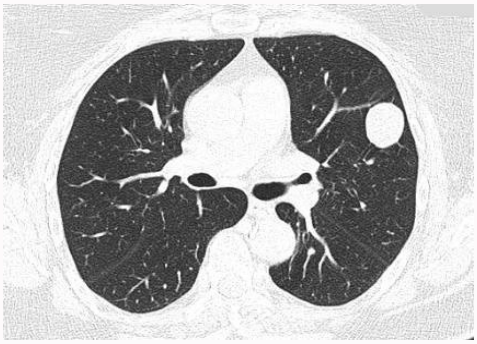

Figure 3: CT scan images.

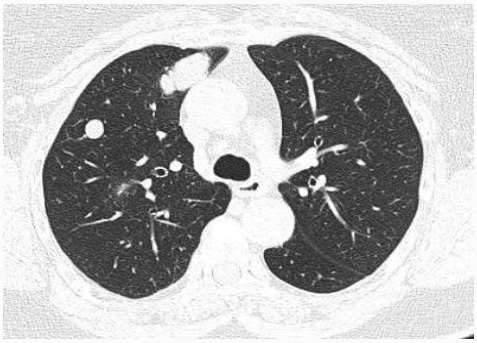

Figure 4: CT scan images.

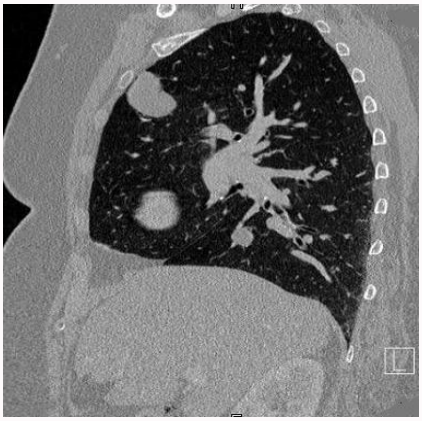

Figure 5: CT scan images.

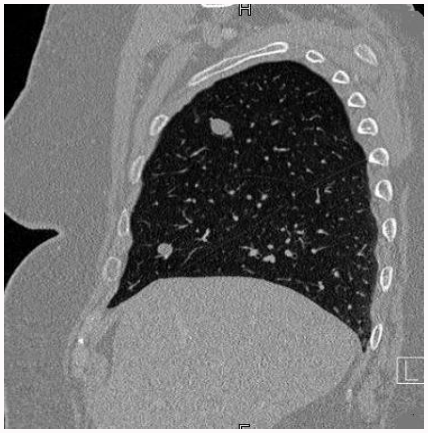

Figure 6: CT scan images.

The patient was also a non-smoker

- Family History: Father HCC of liver
- Work History: Weaver
- Patients History: Gonarthrosis, Hypertension, Repeated Pancreatitis, Status after Gallbladder Removal, Status after Hysterectomy and Unilateral Ovarectomy, Status after Extracorporeal shock wave lithotripsy for nephrolitiasis.

Based on this history, a colonoscopy was performed without greater pathology as early as about 2 years ago during screening.

CT examination was performed with the finding of eight spherical tumors in the lungs of a metastasizing nature affecting all lung lobes. The patient consulted a pneumologist indicating transparietal biopsy of one of the tumors (Figures 1-7).

A CT guided needle biopsy of the tumor was performed without an unambiguously evaluated finding: pulmonary parenchyma with anthracosis and skeletal muscle tissue (Figure 8).

- Spirometry: Normal Finding
- Bronchoscopy: Normal Finding

CEA, CA 15-3 and CA 125 tumor markers were not positive. Thoracoscopic resection of one of the tumors was indicated and planned at an interdisciplinary tumor board (pneumologist, oncologist, surgeon, radiologist and anesthetist). A macroscopically tiny whitish elastic tumor freely releasable from pulmonary parenchyma of the upper lobe of the left lung with cystic component of clear contents was removed surgically.

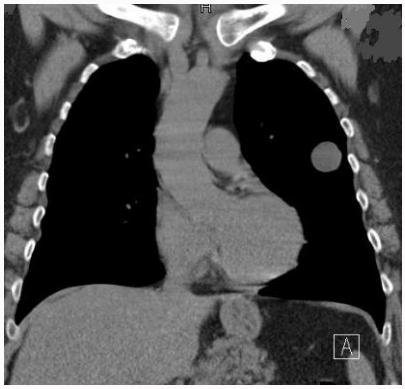

Figure 7: CT scan images.

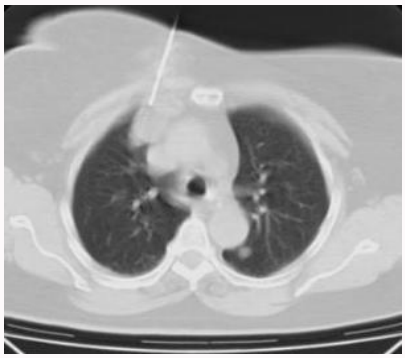

Figure 8: CT guided biopsy.

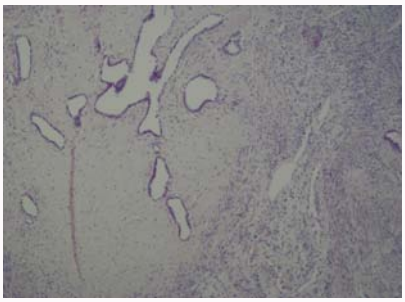

Figure 9: Microscopic picture (100x magnified).

Histology

Collapsed lung tissue with ligamental pleural thickening and a tiny tumor 8 mm × 7 mm × 5 mm. Microscopic spindle cell tumor with small tubules and cysts are filled by cuboidal epithelium. Neither cartilageous, myxomatous nor fat tissue is present. SPP 03 immunological method: Actin, Vimentin positive in mesenchymal part. CK, EMA, TTF-1 positive in epithelial part and CD34 negative, the finding evaluated as fibrolipomatous hamartoma (Figure 9).

Examination of the tissue for estrogen and progesterone receptor positivity with a significantly positive result was done after targeted inquiry (Figure 10).

As the patient was without troubles, had also undergone a hysterectomy in the past with one of the ovaries being removed and there was no current pathology found during the gynecological examination, a conservative approach and dispensary care was recommended. After eight months a spiral CT examination

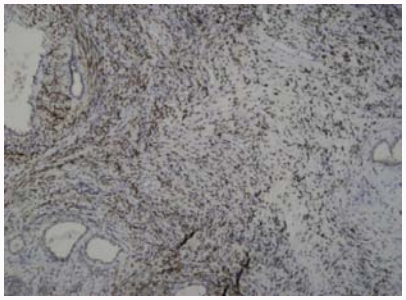

Figure 10: Microscopic picture (hormone receptor positivity).

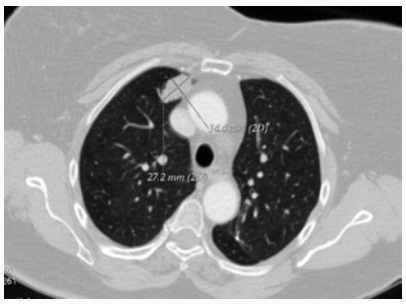

Figure 11: Control CT scan (9 months after the operation) 5 years after the operation was the same.

("watchful waiting") was performed which showed the stability of most of the tumors and surprisingly also a regression of the size of one of the bigger tumors of the right side-apical paramediastinally (27 mm × 14 mm) (Figure 11). After five years a spiral CT examination was performed again which showed multiple lesions in both lung wings, number of stationary, variable in size, some with regressive size and some with progression, all still with size of moderate degree.

The patient was again handed over to the pneumologist for long term dispensary care without any subjective difficulties. Gastroscopic examination with endoscopic ultrasound was recommended as suitable (to exclude unlikely upper gut leiomyoma) but the patient rejected this.

Clonality analysis

For clonality analysis of tumour we used HUMARA clonality assay based on PCR method. Each female somatic cell contains two X-chromosomes. This lethal constitution of double dose of genes on X-chromosome is prevented by inactivation of one of them. Inactivation proceeds in early stage of fatal development. Chemical modification of DNA-methylation-involve many genes on X-chromosome. Gene for human androgen receptor is also regulated by this mechanism. In addition, this gene includes highly polymorphic repetitive sequence, such there is high probability for heterozygous constitution in assessed material. Methylation site is located near this repetitive sequence. One can detect methylation using suitable restriction enzyme which is methylation sensitive. In this case for example HpaII. In the presence of methyl group enzyme cannot cleave DNA. Clonality can be assessed performing PCR of sample digested by restriction enzyme and without. Random inactivation of X-chromosome (polyclonal origin of sample) results in two amplicons of different length (in case of heterozygous constitution of woman cells). On the other hand, inactivation of identical X-chromosome in nearly all cells in sample (monoclonal origin) results in just one amplicon (Figure 12).

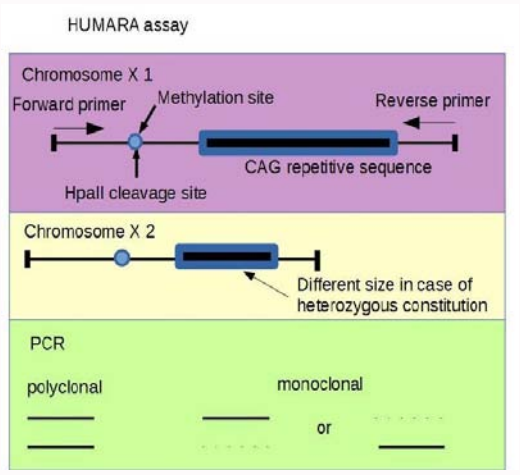

Figure 12: Scheme of HUMARA assay.

Materials and Methods

DNA isolation

We used FFPE 5 µm thick section of tumor and another 5 µm thick section of surrounding healthy tissue. Isolation was done using BiOstic FFPE Tissue DNA Isolation Kit (MoBio Laboratories).

HpaII digestion

Digestion of DNA was done using enzyme HpaII (New England Biolabs) in Buffer CutSmart. A reaction condition was as follows: 1 µl HpaII (10U), 20 µl DNA, 5 µl Smart Cut Buffer, 24 µl water for PCR. Incubation was done overnight at 37°C.

PCR

We prepare PCR mixture by using OneTaq Hot Start 2X master mix with standard buffer (New England Biolabs). Primers at concentration 0.2 µmol per reaction. Forward primer: 5'-TCCAGAATCTGTTCCAGAGCGTGC, reverse primer: 5'-GCTGTGAAGGTTGCTGTTCCTCAT. Settings of PCR conditions: 1.94°C 30 s, 2.94°C 15s, 3.55°C, 4.68°C, steps 2-4 repeat 30X, 5.68°C 5 min.

Amplicon detection

PCR products were analysed by capillary electrophoresis on chip using MultiNA (Shimadzu).

Results

In all samples (tumour digested, tumour undigested, healthy tissue digested and healthy tissue undigested) were seen two bands of size near to 250 bp. It represents heterozygous constitution usable for clonality analysis. There was no difference between digested and undigested samples, so we supposed that origin of tumour is polyclonal.

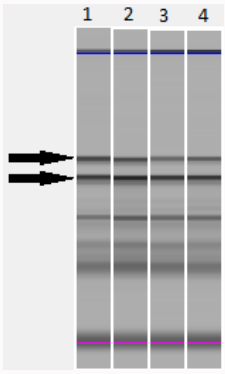

Figure 14: Two bands of size near to 250 bp are seen in all samples treated in different way, 1-Healthy tissue Hpa undigested, 2-Tumour Hpa undigested, 3-Healthy tissue Hpa digested, 4-Tumour Hpa digested.

Figure 13 and 14 two bands of size near to 250 bp are seen in all samples treated in different way, 1-Healthy tissue Hpa undigested, 2-Tumor Hpa undigested, 3-Healthy tissue Hpa digested, 4-Tumor Hpa digested.

Discussion

Pulmonary hamartoma can be manifested as a solitary pulmonary nodule, so called "coin lesion", and also as multiple tumors on a usual chest X-ray image. Coincidental finding is normally indicated for CT examination. Age-old benign hamartoma is often with ossifications and its benign character is usually vivid. Its size does not progress over time and if a patient does not ask or it is not abnormally large, operations are not usually performed. A mini invasive thoracoscopic wedge pulmonal resection should be preferred if there is a solitary tumor and multiple affliction as well. Histologic finding of fibroleimyomatous hamartoma is a great surprise especially in multiple afflictions. Multiple Pulmonary Fibroleimyomatous Hamartoma (MFHP) is a very rare disease and it is not possible to be clinically distinguished from Benign Metastasizing Leiomyoma (BML) and low-grade leiomyosarcoma [14,15]. If some of the examinations (abdominal CT, gastroscopy, colonoscopy, gynecological examination) were not performed before the operation, it is recommended to do so. Indicators of vivid hormonal leiomyoma dependency are spontaneous regression of lung nodules during pregnancy and menopause [16,17]. Hormone receptor examination

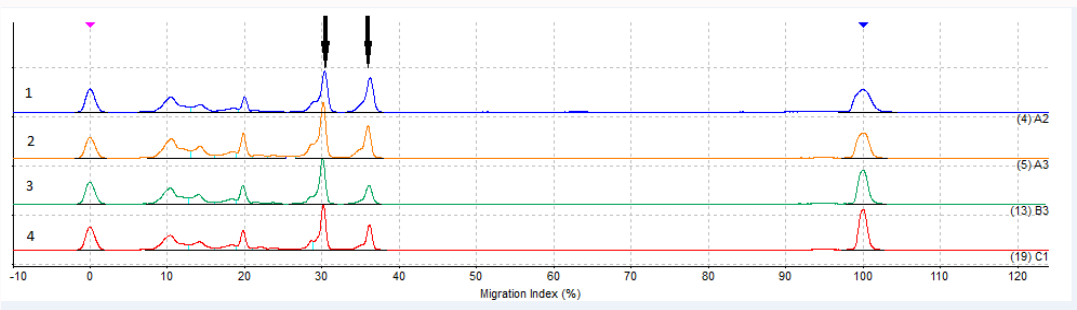

Figure 13: Two bands of size near to 250 bp are seen in all samples treated in different way, 1-Healthy tissue Hpa undigested, 2-Tumour Hpa undigested, 3-Healthy tissue Hpa digested, 4-Tumour Hpa digested.

should precede prediction of the effects of hormonal therapy [18]. Medical castration *via* antiestrogens and surgical performance should be indicated for all tumors with proven hormonal sensitivity whose size progresses significantly over time. Hormonal therapy will probably not lessen the tumors; its task is only to stop its progression. Hysterectomy and adnexectomy of both sides is the method of choice if operated on. Indication for resection even only for some tumors is always compression of the structures in the hilum of the lung and fast growth over time despite hormonal treatment and undergoing of panhysterectomy. Sugawara et al. [2] describes even a very radical approach with staged and repeated enucleation of tumors. 242 nodules (128 from the right lobe and 114 from the left one) were removed from one patient during 12 years. The last enucleated nodule doubled in size during a yearly check. The larger part of this nodule differed from the previous samples and the smaller portion of tissue was identical during histological examination. Finally, it was verified as a soft tissue tumor with uncertain malignant potential from the histological point of view. This case confirms the necessity of both regular checks and active approach to these primarily benign tumors. Potential malignization (however rare it is) cannot be completely eliminated. It is necessary to take into account the age, comorbidity, overall condition and wish of a patient for a suitable approach.

Some authors describe three types of diseases: Lymphangioleiomyomatosis in women, metastasizing leiomyoma in both men and children and multiple pulmonary fibroleimyomatous hamartoma [19,20]. Leiomyomatosis in women occurs in women of reproductive age and has no connection with uterine leiomyoma and is always hormonally sensitive. Lung tumors appear even several years after a hysterectomy for leiomyoma. Some authors consider those extremely well differentiated low-grade leiomyosarcoma [21,22].

MFHP is a very rare disease. As it occurs also in men and children, thus not all cases can be explained by metastasizing uterine leiomyoma. Furthermore, clonal analysis showed nodules are polyclonal in some cases. Metastasizing affection is supposed to be monoclonal [23,24]. If a tumor of the smooth muscle of the uterus is not proved, this tumor should be excluded after targeted inquiry (endoscopy, endosonography) in another location as well, especially in the gastro-intestinal tract [2,23].

Lung lymphangioleiomyomatosis compared to MFPH is a completely different disease during which there is a diffusive proliferation of smooth muscle tissue in lungs especially in women of reproductive age and where tumorous formations are not created. The disease gradually progresses to fatality with pulmonary insufficiency [13].

Differentiated MFHP diagnostics: Metastasizing lesions, hydatid cysts, Echinococcus, Birt-Hogg-Dubé syndrome, Carney syndrome/complex (leiomyoma and stomach GIST, extra-adrenal paraganglioma and multiple pulmonary chondroid hamartoma), Cowden syndrome, Weinberg-Zumwalt syndrome (association with kidney tumors), tuberculomas, granulomas, sarcoidosis and other hamartomatous lesions [11,25-32].

Conclusion

Multiple Pulmonary Fibroleimyomatous Hamartoma (MPFH) is a rare disease which occurs mainly in women of middle age and older but also men and children can be affected. Surprisingly, as a rule the diagnosis is not definitely confirmed until histological examination. It is recommended to obtain a representative MPFH sample via thoracoscopy as the results of transparietal biopsy usually are not absolute proof.

Surgical resection is generally indicated after a coincidental chest X-ray finding and followed by verified non-specific depiction of metastatic lesions on CT scan. MR and PET do not provide further crucial information. During PET examination tumors are without activity and not even a possible primary tumor is identifiable. If hormonal dependency is confirmed, anti-estrogen therapy should be started or gynecological resection considered.

If the patient does not have other problems, the size of the tumors and their amount does not progress with time and hormonal dependency is not proved at the same time, regular dispensary care by a pneumologist is sufficient.

References

1. Logan WD, Rohde FC, Abbott OA, Meltzer HD. Multiple pulmonary fibroleiomyomatous hamartomas. Report of a case and review of the literature. Am Rev Respir Dis. 1965;91:101-3.
2. Sugawara M, Kato N, Endo M, Oizumi H, Motoyama T. Clonal expansion of multiple pulmonary leiomyomatous hamartoma: 12-year follow-up. Pathol Int. 2009;59(11):828-30.
3. Yalçin S, Kars A, Firat P, Demircin M, Tekuzman G, Ruacan S. Multiple bilateral chondromatous hamartomas of the lung. A rare entity mimicking metastatic carcinoma. Respiration. 1997;64(5):364-6.
4. Papla B, Malinowski E. Pulmonary fibroleiomyomatous hamartomas: Report of two cases. Patol Pol. 1991;42(4):128-30.
5. Sargent EN, Barnes RA, Schwinn CP. Multiple pulmonary fibroleiomyomatous hamartomas. Report of a case and review of the literature. Am J Roentgenol Radium Ther Nucl Med. 1970;110(4):694-700.
6. Hassani SN, Nuba R, Bard RL. Fibroleiomyomatous hamartomas of lung: Report of a case. Respiration. 1979;37(4):238-40.
7. Schneider T, Kugler C, Kayser K, Dienemann H. Benign, pulmonary metastatic leiomyoma of the uterus. Chirurg. 2001;72(3):308-11.
8. Tietze L, Günther K, Hörbe A, Pawlik C, Klosterhalfen B, Handt S, et al. Benign metastasizing leiomyoma: A cytogenetically balanced but clonal disease. Hum Pathol. 2000;31(1):126-8.
9. Bachman D, Wolff M. Pulmonary metastases from benign-appearing smooth muscle tumor of the uterus. Am J Roentgenol. 1976;127(3):441-6.
10. Itoh H, Yanagi M, Setoyama T, Shirao K, Yanagi S, Kataoka H, et al. Solitary fibroleiomyomatous hamartoma of the lung in a patient without a pre-existing smooth-muscle tumor. Pathol Int. 2001;51(8):661-5.
11. Nistal M, Hardisson D, Riestra ML. Multiple pulmonary leiomymomatous hamartomas associated with a bronchogenic cyst in a man. Arch Pathol Lab Med. 2003;127(4):e194-6.
12. Hull MT, Gonzalez-Crussi F, Grosfeld JL. Multiple pulmonary fibroleiomyomatous hamartoma in childhood. J Pediatr Surg. 1979;14(4):428-31.
13. Aubry MC, Myers JL, Ryu JH, Henske EP, Logginidou H, Jalal SM, et al. Pulmonary lymphangioleiomyomatosis in a man. Am J Respir Crit Med. 2000;162(2 Pt 1):749-52.
14. Gabka CJ, Müller C, Baretton G, Dienemann H, Schildberg FW. Recurrent multiple leiomyomatous hamartomas of the lung. Chirurg. 1995;66(5):530-3.
15. Kayser K, Zink S, Schneider T, Dienemann H, André S, Kaltner H, et al. Benign metastasizing leiomyoma of the uterus: Documentation of clinical, immunohistochemical and lectin-histochemical data of ten cases. Virchows Arch. 2000;437(3):284-92.

16. Horstmann JP, Pietra GG, Harman JA, Cole NG, Grinspan S. Spontaneous regression of pulmonary leiomyomas during pregnancy. Cancer. 1977;39(1):314-21.

17. Arai T, Yasuda Y, Takaya T, Shibayama M. Natural decrease of benign metastasizing leiomymoma. Chest. 2000;117(3):921-2.

18. Säynäjäkängas O, Maiche AG, Laikka KA. Multiple progressive pulmonary leiomyomatous metastases treated with tamoxifen: a case report with a review of the literature. Acta Oncol. 2004;43(1):113-4.

19. Kaukel E, Burkhardt A, Vogel H. [Multiple pulmonary leiomyomatous hamartosis]. Prax Klin Pneumol. 1983;37(2):71-6.

20. Martin E. Leiomyomatosu lung lesions: A proposed classification. Am J Roentgenol. 1983;141(2):269-72.

21. Burkhardt A, Otto HF, Kaugel E. Multiple pulmonary (hamartomatous?) leiomymomas: Light and electron microscopic study. Virchows Arch A Pathol Anat Histol. 1981;394(1-2):133-41.

22. Canzonieri V, D'Amore ES, Bartoloni G, Piazza M, Blandamura S, Carbone A. Leiomyomatosis with vascular invasion. A unified pathogenesis regarding leiomymoma with vascular invasion. A unified pathogenesis regarding leiomyoma with vascular microinvasion, benign metastasizing leiomyoma and intravenous leiomyomatosis. Virchows Archiv. 1994;425(5):541-5.

23. Wolff M, Silva F, Kaye G. Pulmonary metastases (with admixed epithelial elements) from smooth muscle neoplasms. Report of nine cases, including three males. Am J Surg Pathol. 1979;3(4):325-42.

24. Silverman JF, Kay S. Multiple pulmonary leiomyomatous hamartomas: Report of a case with ultrastructural examination. Cancer. 1976;38(3):1199-204.

25. Ayo DS, Aughenbaugh GL, Yi ES, Hand JL, Ryu JH. Cystic lung disease in Birt-Hogg-Dube syndrome. Chest. 2007;132(2):679-84.

26. Dutta R, Kumar A, Tanveer N, Jindal T, Khilnani GC. Endobronchial fibroleiomyomatous hamartoma: A diagnostic pitfall. Gen Thorax Cardiovasc Surg. 2010;58(7):352-5.

27. Gotti G, Mohamed M, Paladini P, Di Bisceglie M, Volterrani L, Sforza V. Pedunculated pulmonary leiomyoma with large cyst formation. Ann Thorac Surg. 1993;56(5):1178-80.

28. Kato N, Endo Y, Tamura G, Motoyama T. Multiple pulmonary leiomyomatous hamartoma with secondary ossification. Pathol Int. 1999;49(3):222-5.

29. Kiely JL, Dunne B, McCabe M, McNicholas WT. Malignant chondroid syringoma presenting as multiple pulmonary nodules. Thorax. 1997;52(4):395-6.

30. Ozyurtkan MO, Dağli AF, Cakmak M, Balci AE. Multiple cystic pulmonary chondroid hamartomas colonized by Aspergillus species: Report of a case. Surg Today. 2011;41(4):546-8.

31. Zhu H, Huang S, Zhou X. Mesenchymal cystic hamartoma of the lung. Ann Thorac Surg. 2012;93(6):e145-7.

32. Kiryu T, Kawaguchi S, Matsui E, Hoshi H, Kokubo M, Shimokawa K. Multiple chondromatous hamartomas of the lung: A case report and review of the literature with special reference to Carney syndrome. Cancer. 1999; 85(12):2557-61.