Multiple Pulmonary Fibroleiomyomatous Hamartoma

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Abstract

Introduction: Multiple Pulmonary Fibroleiomyomatous 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

Introduction

Multiple Pulmonary Fibroleiomyomatous 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 Fibroleiomyomatous 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.
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.
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 cartilaginous, 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 (“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 (polycional 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).
**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 BioOtic 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'-TCCAGAATCTGTTCCAGAGCCTGC, 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 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-Tumour Hpa undigested, 3-Healthy tissue Hpa digested, 4-Tumour 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 afflication as well. Histologic finding of fibroleimyomatous hamartoma is a great surprise especially in multiple afflications. 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
It is recommended to obtain a representative MPFH sample via thoracoscopy as the results of transpantial 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


