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Pulmonary Sclerosing Hemangioma with Lymph Node Metastasis: A Case Report

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Abstract

Pulmonary Sclerosing Hemangioma (PSH) is a relatively rare lung tumor. Most studies suggest that PSH is benign, but some researchers suggest PSH have malignant potential due to company with lymph node metastasis in certain cases. Here, we reported a case of a 30-year-old female with a solitary mass in her left lung. After a left lower lobectomy and systemic lymphadenectomy was performed, the pathological diagnosis of pulmonary sclerosing hemangioma with lymph node metastasis was given. The immunohistochemistry demonstrated the positive expression of TTF1, EMA in the primary site and metastatic lymph node. Furthermore, AKT1 gene mutation was detected in primary tumor by next generation sequencing. The patient has shown no local recurrence or distal disease in a 1-year follow-up period.

Keywords: Pulmonary sclerosing hemangioma; Lymph node metastasis; AKT1 mutation

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Abbreviations

PSH: Pulmonary Sclerosing Hemangioma; CT: Computed Tomography; 18F-FDG PET-CT: Fluorodeoxyglucose Positron Emission Tomography Computed Tomography; SUV: Standardized Uptake Value; TTF-1: Thyroid Transcription Factor-1; EMA: Epithelial Membrane Antigen; AKT1: AKT Serine/Threonine Kinase 1; mTOR: mechanistic Target of Rapamycin Kinase; CNA: Copy Number Alterations; PI3K: Phosphatidylinositol 3-Kinase; VEGF: Vascular Endothelial Growth Factor

Introduction

Pulmonary Sclerosing Hemangioma (PSH) is a relatively rare lung tumor. This disease was first reported by Leibow and Hubbell in 1956 [1]. Although there are many reviews and case reports about pulmonary sclerosing hemangiomas, cases with lymph node metastasis are still very rare. Here, we described a case of PSH with lymph node metastasis.

Case Presentation

A 30-year-old Asian woman came to our hospital for the treatment of a solitary pulmonary mass in her left lung. The tumor was found in the routine chest CT examination during the treatment of acute pancreatitis. The chest CT examination showed in the left lower lobe, there were multiple high-density nodules with different sizes which subsequently exhibited intense enhancement (Figure 1). The patient did not have cough, hemoptysis, dyspnea, chest pain or other pulmonary symptoms. Tumor markers and physical examination of the patient were both negative. The ^{18}F-FDG PET-CT examination showed multiple soft tissue masses and nodules in the left lower lobe had partial central necrosis and abnormal tracer concentration. The nodules, of which the SUV max was 6.7, were considered to have low-grade malignancy possibly. Besides, the bilateral hilar lymph nodes, of which the SUV max was 3.0, were considered to be reactive lymph node hyperplasia. The patient underwent thoracoscopic resection of the left lower lobe and systemic lymphadenectomy under general anesthesia.

Macroscopically, the sample of the left lower lobe of lung was about 13 cm × 8 cm × 4 cm. A 9 cm × 5 cm × 4 cm lobulated ill-defined tumors with a grey-white section can be found in the sample. The pathology showed that the tumor was composed of round cells and surface cells. The immunohistochemistry demonstrated the positive expression of TTF-1 (Thyroid Transcription

Table 1: The review of pulmonary sclerosing hemangioma with lymph node metastases.

Author	Age	Gender	Primary tumor location	Metastatic lymph node, n	Site of Metastatic lymph node
Tanaka I 1986 [19]	22	male	RLL	1	hilum
Devouassoux-Shisheboran M 2000 [6]	18	female	LLL	2	hilum
Yano M 2002 [20]	67	female	RLL	5	hilum mediastinal
Kim KH 2003 [21]	19	female	LLL	11	hilar interlobar intrapulmonary
Miyagawa-Hayashino A 2003 [22]	10	female	RML	1	regional
Miyagawa-Hayashino A 2003 [22]	45	female	RUL	3	hilum
Miyagawa-Hayashino A 2003 [22]	45	male	LLL	1	mediastinal
Miyagawa-Hayashino A 2003 [22]	56	female	LLL	1	intralobular
Chan NG 2003 [23]	19	male	LUL	2	interlobar
Kim GY 2004 [24]	37	female	LLL	1	supraclavicular
Wang L 2005	56	female	RLL	ND	hilum
Katakura H 2005 [25]	35	male	LLL	1	mediastinal
Li JC 2006	70	female	LLL	1	mediastinal
Jiang ZN 2007 [26]	59	female	RLL	1	interlobar
Vaideeswar P 2009 [27]	23	male	RUL	several	hilum
Chien NC 2009 [28]	18	male	LUL	1	mediastinal
Adachi Y 2014 [11]	40	female	LLL	1	mediastinal
Xu HM 2015 [12]	26	female	RUL	1	hilum
Pokharel S 2016 [29]	33	female	LLL	1	not available
Soo IX 2017 [30]	40	female	RLL	5	intraparenchymal
Present case	30	female	LLL	11	interlobar hilum mediastinal

Factor-1) EMA (Epithelial Membrane Antigen) in the primary tumor with round and surface cells (Figure 2), as well as the positive expression of TTF-1 in the metastatic lymph node (Figure 3). According to clinical manifestations and histological features, the patient was diagnosed as pulmonary sclerosis hemangiomas with lymph node metastasis. The patient had no signs of local relapse and distant metastasis in 1-year follow-up after surgery despite of lymph node metastases.

Furthermore, in order to explore the molecular structure of this tumor, the mutations of 295 tumor-related driver genes are detected by a high-throughput sequencing test (Guangzhou Burning Rock Biotechnology Inc. China). All 295 genes are described as previously report [2,3]. We use the patient blood DNA as basic line to analyze the tumor tissue, after ruling out genetic variations, 2 tumor-related somatic mutations of AKT1 and mTOR are confirmed, of which AKT1 missense mutation with abundance of 34.6% and mTOR missense mutation with abundance of 5.3%. These gene analysis results were consistent with the current molecular studies.

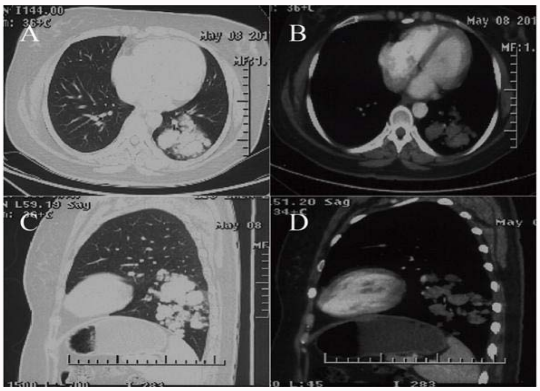

Figure 1: Computed tomography scans of chest. There were multiple high-density nodules with different sizes which subsequently exhibited intense enhancement which located in the lower lobe of the left lung.

Discussion

Pulmonary sclerosing hemangioma is a relatively rare lung tumor, which was first reported by Liebow and Hubbell in 1956 [1]. PSH, which occurs in Asia mostly, primarily affects middle-aged women with the male and female prevalence ratio of 1:5 [4,5]. The tumors are mostly found in routine CT examination without obvious symptoms, and the size of PSH is mostly between 0.3 cm to 8cm. There is usually a regular well-defined round or oval tumor without obvious lobulation or speculation in chest CT. The tumor usually showed faint uptake of contrast agent with mild elevation of SUV max, which indicates the possibility of low-grade malignancy. It is more difficult to differentiate PSH with enlarged Mediastinal lymph node from lung cancer, whence pathology plays a crucial role in the diagnosis of PSH.

PSH is mainly composed of surface cells and round cells. Immunohistochemical staining showed that both of the two cells expressed epithelial membrane antigen and thyroid transcription factor-1, of which TTF-1 expressed specifically in mature type II alveolar cells, Clara cells and embryonic alveolar epithelial cells. Further studies found that the expression of CK pan, CK-7, CAM5.2 and surfactant proteins were only positive in the surface cells, and barely he in round cells [6-8]. Therefore, the researchers concluded that the

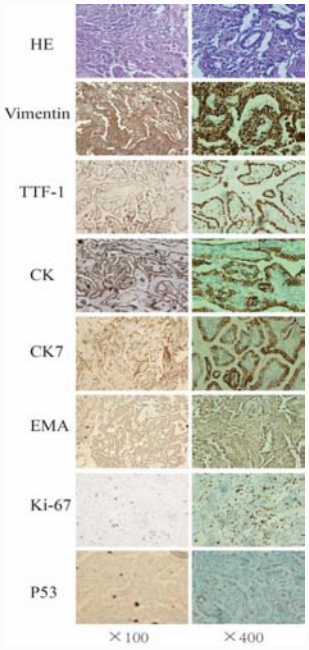

Figure 2: Pathological characteristics. Pathological characteristics demonstrated by H&E staining and Immuno-histochemical staining in the primary tumor. Immuno-histochemical staining detected epithelial membrane antigen thyroid transcription factor-1 was detected in both the surface cells and the round cells. Vimentin was detected in the round cells and CK, CK7 was detected in the surface cells. The Ki-67 labeling index was near 5.9% and the P53 labeling index was <5%.

surface cells were induced by reactive hyperplasia of type II alveolar cells, whereas round cells were most likely produced by pluripotent primitive respiratory epithelial cells [9]. The study found that in some female patients with sclerosing hemangiomas, the expression of estrogen and progesterone receptor play a significant role in not only promoting transformation from the primitive epithelial cells to the of surface cells and round cells, but also promoting tumor growth, differentiation and surfactant production [6,10].

In the past pulmonary sclerosing hemangioma was considered to be benign. However, with more and more cases about PSH with lymph node or liver metastases reported [11,12], many researchers believe that PSH have malignant potential. There is also another reported case which showed relapse as a bone metastasis after surgery, which initially showed node metastasis [13]. As the same as benign tumor, the prognosis of PSH is good. Surgical resection of the lesion is the main treatment for PSH [14]. The conventional procedures include partial lung resection, pulmonary lobectomy, and systemic lymphadenectomy in case of lymph node metastases. The preoperative diagnosis of PSH is difficult, for it is usually misdiagnosed as adenocarcinoma by intraoperative frozen section. Therefore, postoperative histological and immuno-histochemical examinations are the main way to diagnose PSH.

The literature search revealed a total of 21 cases reported PSH with lymph node metastases, of which 17 were described in English and 4 were in Chinese. The patients' age was between 10 to 70, with an average age of 37.5 and a median age of 36. In these cases; there were 6 males and 15 females, with a gender ratio of 2:5. The average age of males and female was 27 and 40.7, respectively. Of the 21 cases, we found 10 primary tumors were in the left lower lobe, 3 were in the left upper lobe, 2 were in the right upper lobe, and 1was in the right

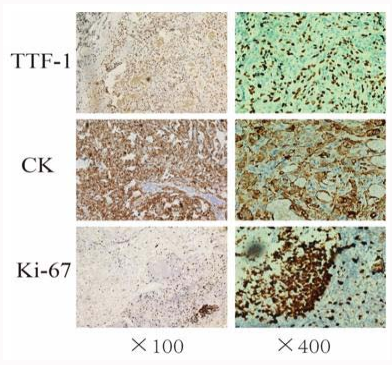

Figure 3: Pathological characteristics. Pathological characteristics demonstrated by Immuno-histochemical staining in the metastatic lymph node. The positive expression of TTF-1 and CK was detected and the labeling index of Ki-67 was near 7.5% in metastatic site.

middle lobe, and 5 was in the right lower lobe. Nine of the patients had hilar lymph node metastases, and seven of them had Mediastinal lymph node metastases. Earlier, Devouassoux Shisheboran et al. [6] conducted a detailed analysis of 100 PSH cases. Among these 100 patients, patients were between 16 to 76 years old, with an average of 46 years old. There were 17 males and 83 females, with a gender ratio of 1:5. For the location, 46% of the tumors were found in the left lung and 54% were found in the right lung. According to the data statistical analysis, it indicates that PSH mainly occurs in the middle-aged women, and there is no significant difference in the location of the tumor.

According to the case review, pulmonary sclerosing hemangiomas have the potential of malignancy. Literature review and analysis suggest that lymph node metastasis may be related to the age, sex, tumor size and location of the tumor. Although PSH can be with lymph node metastases, there is no significant difference in prognosis between patients with or without lymph node metastases. Currently, the complete surgical resection of the tumor is still the only effective treatment for PSH.

Although the histogenesis of Pulmonary Sclerosing Hemangioma (PSH) is thought to originate from respiratory epithelial, the molecular mechanisms that mediate its occurrence and development are not clear. Studies showed that highly frequent AKT1 gene mutation could be found in PSH including somatic mutations and copy gains. As we knew, the protein kinase v-AKT Murine Thymoma Viral Oncogene homolog (AKT) plays an important role in cell survival and proliferation, which functions downstream of PI3K [15]. Recurrent AKT1 mutation was first reported in breast cancers [16]. However, the frequency of AKT1 mutations in PSH was much higher than other tumors [17]. Although AKT1 mutations in PSH are relatively common, approximately 40% of PSHs exhibited neither driver mutation nor CNA mutation (Copy Number Alterations); this result showed that the epigenetic and genetic origin of PSH had not been determined [17]. Some studies showed that aberrant mTOR signaling may play a role in the development of PSH, and its vascular nature may be due partially to high levels of VEGF caused by dysregulation of mTOR signaling [18]. Therefore, PI3K/AKT/mTOR signaling pathway may play a role in the occurrence and development of PSH, but the mechanism of action is still not clear. However, the mutation of AKT1with high abundance was also found in the gene test of this patient, which might provide a guide for the treatment of PSH in the future.

Conclusion

The preoperative diagnosis of PSH is difficult, postoperative histological and immuno-histochemical examinations are the main way to diagnose PSH. The PSH with lymph node metastasis is relevantly rare. The effective treatment for PSH is surgical resection and it is rarely relapse or metastasize after surgical resection. Completely surgical resection should be the first choice of the treatment due to the risk of malignancy. This uncommon case we delivered shows several gene mutations, including AKT1missense mutation and mTOR missense mutation. Although the medical treatment focus on gene target is not a mainstream, the gene research and further study of PSH is necessary and meaningful.

Ethics Approval and Consent to Participate

This case was approved by the ethics committee of our institution (Tianjin Medical University General Hospital).

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Author's Contributions

FR, ZH, ZZ, GC and JC wrote this manuscript and analyzed all data. FR, ZH, ZZ, ZH, XX, LH provided medical care for the patients and collected the data. GC and JC revised the article. All authors read and approved the final manuscript.

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