Sygnatura: Pol J Radiol, 2007; 72(1): 36-43

Polish Journal of Radiology
www.PolRadiol.com
ORIGINAL ARTICLE

Otrzymano: 2006.03.14
Zaakceptowano: 2006.06.20

Histological and radiological diagnostics of the pulmonary hamartomas

Ewa Kaznowska[1], Wiesław Guz[2,5], Radosław Ramotowski[2,5], Wojciech Kądziołka[3], Andrzej Kulig[4]

[1] Department of Pathomorphology, Specialistic Hospital of Tuberculosis and Pulmonary Diseases in Rzeszow, Poland
[2] Department of Radiology, Specialistic Hospital of Tuberculosis and Pulmonary Diseases in Rzeszow, Poland
[3] Department of Thoracosurgery, Specialistic Hospital of Tuberculosis and Pulmonary Diseases in Rzeszow, Poland
[4] Departament of Clinical Pathomorphology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[5] Faculty of Health Science, Rzeszow University, Poland

Author's address: Ewa Kaznowska, Specialistic Hospital of Tuberculosis and Pulmonary Diseases, 35-241 Rzeszow, Rycerska 2, e-mail: e.kaznowska@op.pl

Summary

Background: The objective of our study was to compare histological and radiological images of the hamartomas (H) localized in lungs. The analysis consisted of 54 cases, which were diagnosed and operated on in Specialistic Hospital of Tuberculosis and Pulmonary Diseases in Rzeszow in years 1999-2005. Average age of patients, mostly men, was 55 years. H was diagnosed accidentally in 75% of cases, and was not related with other diseases. Histologically, cartilaginous or fibro-cartilaginous tissues dominated in H structures; H with adipose tissue component appeared rarely. Diameter of H was less than 3 cm in most of the cases. All H were located peripherally in the chest and showed no preferences to the localization. Computed Tomography demonstrated calcifications in 30% of H. As for etiology, clinical and histological aspects of the H and also differential diagnosis of the radiological features were presented.

Key words: Pulmonary hamartoma • Chest X-ray • Computed Tomography

PDF file: http://www.polradiol.com/fulltxt.php?ICID=468398

Background

Hamartoma (H) is a lesion composed of mature tissues (muscular, fibrous, cartilaginous, osseous and adipose tissues) which do not form organized structures [1] (fig. 1, 2).

They arise from multipotential mesenchyma which shows the ability to differentiate into mature tissues. Singular cases of transformations into malignant tumors have been described [2, 3, 4]. It is now believed that hamartomas are not congenital lesions and they occur in individual lives as a result of unknown pathogenetic factors [5]. In some cases familial tendency for H incidence was observed, especially in lungs. Inflammations were considered as the initiative factors for proliferation in these cases, although recently a relation between gene mutations and H occurrence has been proved. Some claim that smoking can influence the development of H [6, 7]. However, H can grow in every kind of organ. The occurrence of one tumor or multifocal infiltration of several organs is the base of varied clinico-morphological pattern.

H located in the lungs are the most common benign lesions and constitute about 30% of all benign pulmonary tumors [8, 9]. Half of them take the form of solitary peripheral nodules of slow growth (solitary pulmonary nodule – SPN) [8]. The incidence in population is estimated for 0.25% [10], two to four times more frequent in men than women [11]. The age of patients varies from 30 to 70 years, the peak occurrence being in the 6th decade of life [12, 13] but the important thing is – they do not occur in neonates, infants and small children.

In most cases they grow as solitary tumors. Hamartomas are located in peripheral regions of lung as well as inside the bronchial tubes and show no significant tendency for

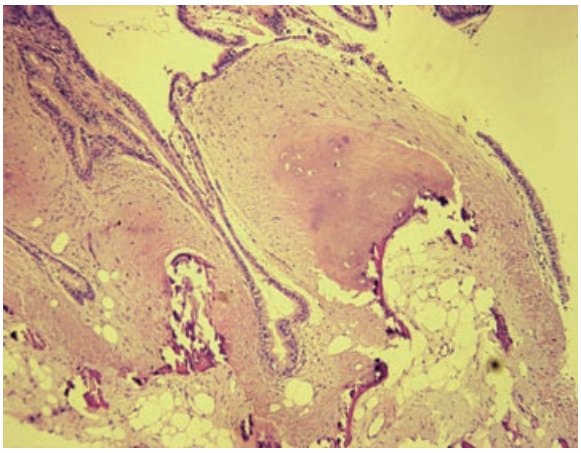


Figure 1. Cartilaginous structure of the hamartoma with fatty tissue and calcifications components.

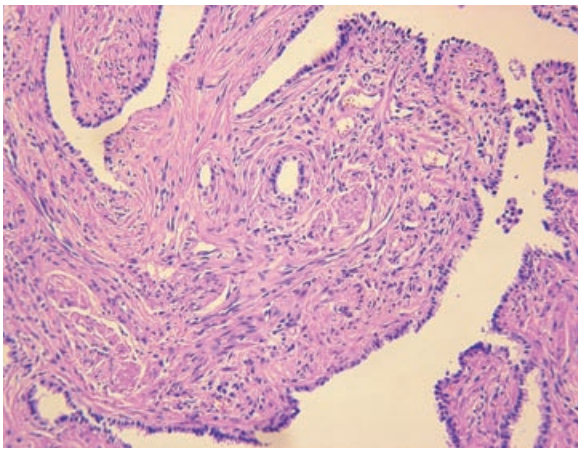


Figure 2. Hamartoma compound with fibrous and muscular tissue.

occupying certain lobes or a lung [11, 12]. The average size varies from 1.5 to 3 cm [11, 12] and does not depend on anatomical localization but shows certain level of dependency on advancing age of a patient [12]. Endobronchial lesions constitute 10–20% of pulmonary hamartomas [10, 13, 14].

In literature it is emphasized that even the biggest nodules located in the pulmonary parenchyma give no clinical symptoms [11, 14, 15] while those in the bronchi often cause cough, hemoptysis, fever, respiratory disfunction or pneumonia [9, 10, 16, 17]. The course of H is mild but the treatment of choice is surgical resection of the lesion [6, 11, 12, 14, 15]. This is usually because in many centers the possibility of malignant development (peripheral carcinoma) or focal inflammatory lesion (e.g. tuberculoma) is taken into consideration in cases of indefinite diagnosis of lesions. If the location is endobronchial, clinical symptoms (hemoptysis, atelectasis, inflammation of segment of a lung) dependent on the level of bronchial occlusion, become a direct indication for surgical treatment.

No matter if the hamartomas are located in peripheral pulmonary parenchyma or inside the bronchi, they show minor structural differences [18]. Peripheral H are represented by multilobular solid tumors of oval or round shape with smooth or irregular contours [19], embedded in pulmonary parenchyma. Their consistency depends on the proportion of tissue elements. On the contrary, the endobronchial hamartomas take the form of polyp growing into the lumen of bronchi [18, 19] and occlude it to some extend.

Hamartomas are usually built from mature cartilaginous tissue, which forms clusters surrounded by variable cell-rich fibrous and myxomatous tissue mixed with focuses of adipose tissue and fibers of smooth muscles [10]. Focuses of calcification and osteoplasia or proliferation of thin-walled blood vessels are less often. The stroma of tumor is covered with bronchial cylindrical epithelium which can form indentations or fissures. Some Hs are only built of fibrous and muscle tissues [20]. In others an immature mesenchyma forming polycyclic confluent nodules is observed. They might grow or undergo cystic degeneration in subsequent observations (the so-called mesenchymal cystic hamartomas) [21, 22, 23]. Structures similar to placental villi are identified in some hamartomas [24]. In such cases they are peculiar villuslike papillary projections, the stroma of which is built of myxolipomatous tissue covered with epithelium. Such structures are usually observed in emphysematously altered pulmonary parenchyma. Focuses of macrophages containing brown pigment can often be found in the lumen of pulmonary alveoli near the hamartoma.

Formation of multiple hamartomas occupying central nervous system, kidneys, skin, lungs and heart is one of the morphological exponents of tuberous sclerosis complex (TSC). In population it occurs with frequency of 1:6000 [25] and is inherited autosomally as a dominant trait. It is caused by TSC 1 and TSC 2 gene mutations. TSC related hamartomas rarely become malignant. The exception is renal-v-cell carcinoma, which develops from renal hamartoma [26]. The renal H in form of angiolipoma is often associated with tuberous sclerosis and as such is known as Bourneville's syndrome [27].

On the other hand, multiple Hamartomas ocurrence can be a part of Carney's triad – a rare syndrome of unknown etiology which occurs most often in young women. The triad includes pulmonary chondroma, gastrointestinal stromal tumor (GIST) and extra-adrenal phaeochromocytoma [28].

Due to the fact that hamartomas are asymptomatic in most cases, they are usually diagnosed accidentally during plain radiological examinations of the thorax [6]. Radiological image usually shows oval or round shadow with smooth contours, sometimes with calcification focuses [9, 29].

The plain radiological examination of the chest often reveals a round shadow in a lung. The exam is most often performed in typical – anteroposterior and lateral – projections. Other projections (oblique) or thoracic scopy can be used for visualizing indistinct or doubtful lesions. Radiological evaluation is easier when the location of nodule is far from the diaphragm, mediastinum or thoracic wall, and the easiest in intercostal space. The RTG of the chest usually reveals H as a solitary, well circumscribed, round or (rarely) oval nodule with diameter of 4 cm (median 2 cm), localized peripherally in lower pulmonary lobes (fig. 3). Calcifications often placed centrally, with characteristic arrangement resembling popped corn ("popcorn sign") are stated in 10–15% of H cases [32, 33].

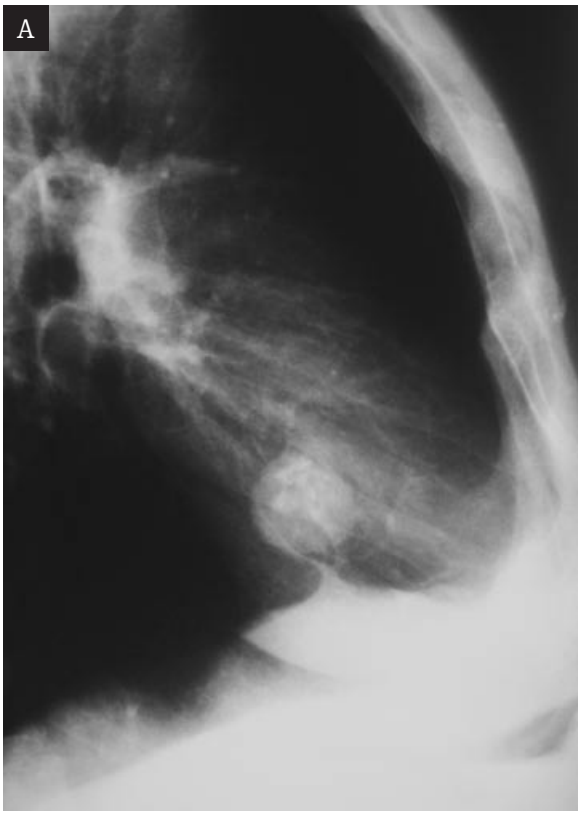


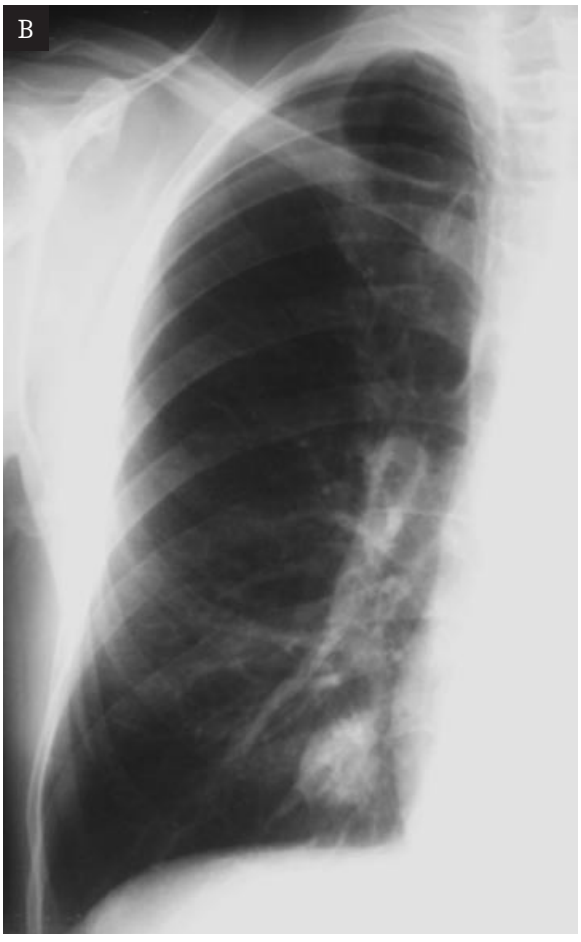
Figure 3. Typical X-ray image of the pulmonary Hamartoma.

Computed tomography with contrast agent administration and densitometry enables a more precise delineation of morphological features of a fortuitously discovered nodule. Typical representation of H in CT exam is a solitary nodule of round or oval shape and low density (especially if it contains larger amount of adipose tissue), with sharp edges, localized peripherally in lower lobes, well – circumscribed and containing single or popcorn-like calcifications (fig. 4) [30, 31, 32].

Materials and methods

The study comprised 54 patients including 33 men and 21 women aged 24 – 74. Average age of both, men and women, was 55 years. All patients were diagnosed and operated on at Specialistic Hospital of Tuberculosis and Pulmonary Diseases in Rzeszow in years 1999–2005. RTG of lungs was always performed in anteroposterior and lateral projection, and 18 patients underwent additional CT exam with the use of typical protocol, only in a few cases with HRCT protocol. 8 patients underwent bronchoscopy, while bronchial contents were collected from other 3 for cythological examination. Bronchial specimens were not examined.

The preoperative diagnostics did not include thin-needle aspiration biopsy because of small dimensions of the nodule or lack of patient's agreement. In no case was the definite diagnosis based on clinical, imaging or cytomorphological examinations made before the operation. All patients underwent thoracotomy with tumor resection. All lesions were examined intra-operatively. The surgical procedures of H resection constituted 5.8% of all thoracotomies conducted for neoplastic reasons at the Department of Thoracic Surgery. In 51 cases sparing operations were performed (simple resection of the nodule, marginal or wedge resection). In 3 cases the decision of pulmonary lobe resection was made due to big dimensions of the lesion. The operations were carried out in accordance with conventional standards. They proceeded without complications.

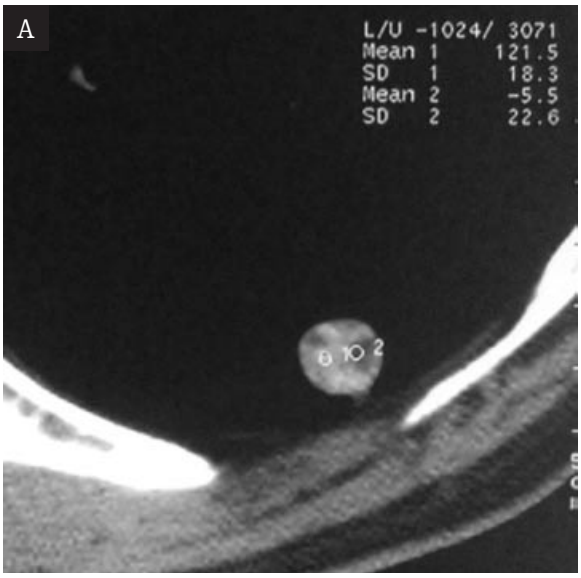


Following check-up examinations after 7, 14, 21 days and 1, 2, 3, 6 and 12 months revealed no permanent complications, no local recurrences, no signs of malignant process. The operative material was assessed by means of histological and immunochemical examinations.

Results

Patients were divided into three age groups (table 1). The dominating group comprised patients aged 40–60 (62%). 61% of patients were male, but this ratio was higher in groups aged 40–60 and over 60, while in the group aged 20–40 the proportion of men and women was equal (50%). However, it was a small group of patients (7.5%).

In 72% of patients no respiratory troubles were stated at the time of H-type lesions detection and the RTG of lungs was performed as a periodic examination or in relation to other diseases. Other patients complained of cough (9%), dyspnea (7.5%), chest pain accompanied by weakness (4.5%) and in single cases – of subfebrile body temperature



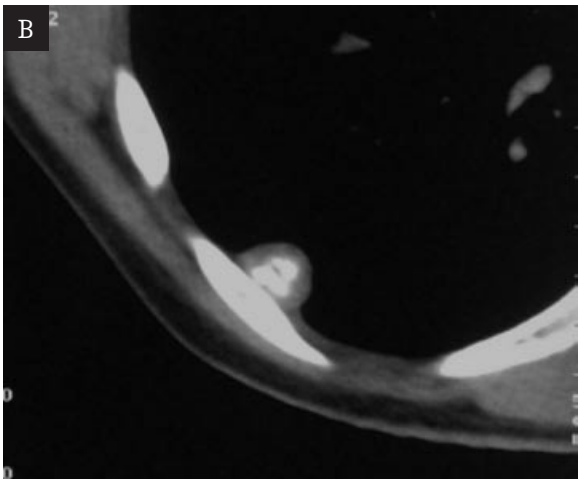


Figure 4. Different morphology of hamartoma (adipose tissue, calcificationes) visible in CT examination.

or hemoptysis. In one case of endobronchial H the patient suffered from dyspnea and cough. Among the coexisting diseases the most common were arterial hypertension (18.5%), less often – chronic ulcer disease and nodular goiter (5.5%). 30 patients out of 54 answered the question concerning smoking cigarettes – the number of nonsmokers (53%) almost equaled the smokers (47%).

All patients underwent radiological examination of the thorax which revealed lesions in form of round or oval solitary shadows, with smooth contours and well-circumscribed from the surrounding tissues. In all cases the localization was peripheral, regular, without predilections to a certain segment of lung (table 2).

The size of focuses varied from 6 mm to 7 cm, but most of the lesions did not exceed 3 cm and only in 6 patients (10.1%) the nodules were equal or bigger than 3 cm. There is a slender correlation between the advancing age of patients and size of the nodule. Small nodules up to 1 cm were more frequent in women (table 3). It was noted that in the group of H containing adipose tissue the diameter of nodules did not exceed 1 cm, while in the group of nodules over 3 cm mixed or cartilaginous forms were dominant. During RTG examinations calcifications were found in 20% of cases but in patients who underwent the CT the percentage grew to 30%. The calcifications found

Table 1. Division of the patients with Ph for age and sex groups.

Age groups	Sex		Total	%
	female	male		
Up to 40 y.	2	2	4	7,41
41-60 y.	13	21	34	62,96
over 60 y.	6	10	16	29,63
Total	21	33	54	100,00

Table 2. Localisation of Ph in lobes and lungs.

Localization	Upper lobe	Lower lobe	Central lobe	Total
Right lung	10	13	4	27
left lung	14	13	0	27
Total	24	26	4	54

Table 3. Relations beetwen dimensions of the Ph and age or sex groups.

Age groups	dimensions			total	% to 1 cm/manpower of the group
Sex	Up to 1 cm	1–3 cm	over 3 cm		
Up to 40 y.	1	3	0	4	25%
41-60 y.	6	23	5	34	17,65%
over 60 y.	3	12	1	16	18,75%
Total	10	38	6	54	18,51%
women	7	12	2	21	33,33%
men	3	26	4	33	9,09%
Total	10	38	6	54	18,51%

Table 4. Tissue compounds of Ph in correlations with dimensions of the Ph and sex of patients.

HP results	Sex		Total	Dimensions			Total	HP % of a group
	F	M		Up to 1 cm	1 - 3 cm	over 3 cm		
C	7	21	28	4	22	2	28	51,85
F	3	1	4	2	1	1	4	7,41
F-C	5	9	14	2	11	1	14	25,93
F-C-A	3	2	5	0	3	2	5	9,26
F-A	3	0	3	2	1	0	3	5,55
Total	21	33	54	10	38	6	54	100

Compounds: C – cartilaginous tissue, F – fibrous tissue, A – adipose tissue

at CT were usually located peripherally, they were solitary, regular, point or oval and if they were multiple they showed tendency for cumulating. However, the so-called "popcorn sign" was extremely rare.

None of the nodules showed focuses of decomposition or air cavities. The level of contrast enhancement of focuses was moderate and varied from 0–15 HU and depended largely on histological structure of the nodule. In cases when lesions contained adipose tissue (about 15%) their density was low (-20 to + 5 HU) and enhancement poor or none. The density of cartilaginous or fibrous lesions observed on native scans varied from 20 to 40 HU but they showed better enhancement in some cases (up to 55 HU).

As for histology, the nodules contained different proportions of cartilaginous, fibrous and adipose tissues (table 4). Over half of the nodules (52%) were made of exclusively cartilaginous tissue, while 87% contained cartilaginous tissue in association with other tissues. Fibrous tissue was the only building material in 7.5% of lesions, but occurred in 48% of mixed forms. Adipose tissue appeared only in mixed forms – that is in 15% of nodules. In women we observed higher incidence of H with clear fibrous structure (75%) and domination of nodules containing adipose tissue (75%). In men, on the other hand, nodules of cartilaginous structure were twice as frequent (59%) as in women (28%). Mixed forms occurred equally often in men and women.

In one case (1.8%) H grew endobronchially. The nodule with dimensions of 1.5 x 1.5 x 2.5 cm, made of the fibrous and adipose tissues was located in the lower lobe of left lung (fig. 5).

8 patients underwent preoperative bronchoscopy which showed traces of diffuse inflammatory lesions of bronchial mucosa.

All patients were operated on with the use of thoracotomy and sparing surgeries based on enucleation of nodule or wedge resection of pulmonary parenchyma.

Discussion

Radiological images enable H diagnosis of high accuracy provided that the nodule is round with smooth contours, smaller than 3 cm, shows presence of "popcorn" calcifications (cartilaginous calcifications) and is well-circumscribed from the surrounding tissues. Differentiating diagnosis includes both the benign and malignant lesions. Although

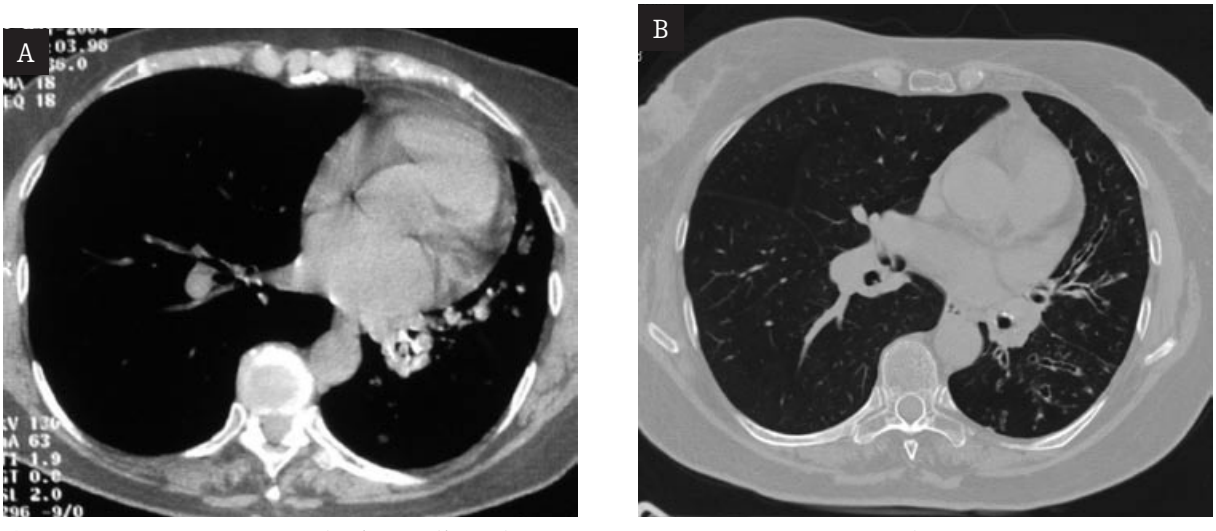


Figure 5. Endobronchial hamartoma before (on the left) and after operation – bronchiectases are visible on the left lower lobe.

Table 5. Differentiations of the Ph in dependencies from radiological cryteria.

Radiological criterion	Hamartoma	Other benign lesion	Malignant neoplasm
size	Up to 3 cm	Up to 3 cm	50% up to 2 cm, Most over 3 cm
structure	Oval or round shape well-circumscribed smooth contours	Oval or round shape well-circumscribed smooth contours	Not well-circumscribed, dim contours, metastases often well circumscribed
calcifications	in 20-30% punctual, oval, rarely in form of the so-called pop corn sign	diffuse or „central nuclei" (tuberculoma)	excentric in 10% of primary pulmonary carcinomas (carcinoid), diffuse in metastases of osteosarcoma, osseous metaplasia in malignant tumors
cavernous space	rarely – the so-called mesenchymal cystic hamartoma	Pulmonary absces, tuberculoma	frequent
adipose tissue	in 15% of H	lipoma, lipoid pneumonia	none
satellite nodules	none	granuloma	bronchiogenic carcinoma
contrast enhancement	low	rarely	strong
growth	none or duplication time – 2 years	none or duplication time – 2 years	duplication time – 100 days

the size of H usually does not exceed 3 cm, half (50%) of solitary nodules sized 2–3 cm located peripherally in the lung have malignant characteristics. Round or oval shape and well circumscription in most cases indicate benign lesions, while dim contours, spiculations, satellite focuses suggest malignant infiltration.

Although solitary metastases from extra-pulmonary focuses often show similar peripheral location and structure, the multiple forms of H are also observed. Calcifications do not determine the diagnosis of H as the RTG examination shows them only in 20% of cases and CT – in 30%. Calcifications are also found in tuberculomas but they are usually scattered or focal – in form of "central nucleus". Eccentric calcifications are typical for 10% of primary pulmonary carcinomas and frequent in carcinoids, but diffused in metastases of osteosarcoma [8, 30, 34]. Focuses of osseous metaplasia occur in some malignant tumors. Cavernous space usually indicates necrosis and dissolution in a malignant neoplasm, but it is also typical for pulmonary abscess and frequent in tuberculoma. Only a rare type of H, the so-called mesenchymal cystic hamartoma, can have cavernous structure, clearly visible in RTG examination. Doubtful lesions in RTG require further diagnostics (table 5).

Computed tomography (CT) is a more sensitive examination than RTG of lungs. The usefulness of CT in evaluation of solitary pulmonary nodules detected fortuitously with RTG lies in stating whether the lesion is a nodule or artifact. In case of confirmation it enables precise definition of its shape, size, circumscription and presence of satellite focuses (fig. 6, 7). CT is useful for monitoring the lesion's growth dynamics in control examinations as well as for estimation of duplication time, which is long for benign tumors (including H) and amounts for at least 200 days and 100 days in case of malignant lesions [8, 30, 34]. It is possible to measure the density after intravenous contrast administration during the examination, and then to compare it with a reference model. CT is useful for detecting the calcifications within the H, allowing its precise appearance and size description. Focuses of density over 100 HU, visible on native scans and qualified as calcifications, can be invisible on RTG images. In general, CT visualizes typical calcifications in 25% of hamartomas.

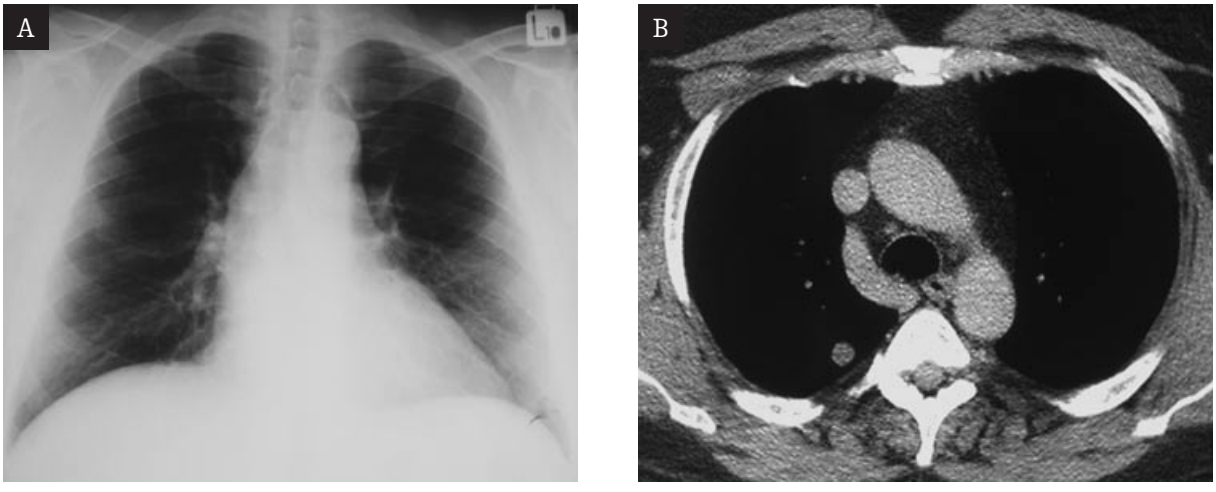


Figure 6. Comparison of the X-ray and CT images of the pulmonary hamartoma – difficulty of identification of the lesion on chest X-ray is visible.

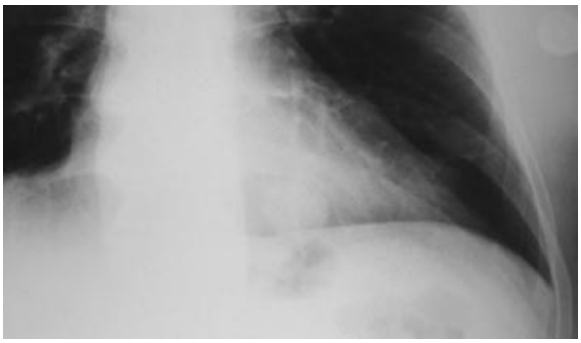


Figure 7. Pulmonary hamartoma on the chest X-ray in difficult to diagnose location.

Owing to density measurements detection of adipose tissue is possible in 30 % of H cases as this type of tissue presents a characteristically low density (around -70 to -110 HU). This type of tissue is present in benign lesions (e.g. lipoma) which occur in lungs far less frequently than H but is never found in malignant neoplasms. Analysis of CT image followed by density measuring after contrast administration allows defining the character of a solitary nodule and answering the question, whether the tumor is benign or malignant. Benign lesion is characterized by low uptake of contrast agent and low density (< 15 HU). If the density is over 20 HU the risk of malignant lesion increases. In such case, the CT examination can help define the level of its advancement. Computed tomography (especially spiral and multi-slice CT) is the method of choice in evaluation and monitoring the peripheral pulmonary nodules as it gives a precise image of all structures of pulmonary parenchyma, has high linear resolution and short time duration, owing to which the artifacts can be evaded eliminated [30, 31, 32].

The use of Positron Emission Tomography (PET) with fluoro-deoxy-glucose (FDG) for differentiating benign and malignant lesions is still under research. High metabolism accompanied by higher FDG consumption indicates a malignancy of the nodule [33]. The unquestionable advantage of the method is its noninvasiveness and rare presentation of false negative results. Yet, it is an expensive method of low accessibility and bares a risk of 10–15% of falsely positive results. The minimal size of nodule necessary for evaluating its metabolism is 1 cm.

In order to numerous limitations arising from the structure of pulmonary parenchyma as well as from technical aspects the magnetic resonance is not widely applicable in diagnostics of small peripheral pulmonary nodules which are not connected to mediastinal structures and/or thoracic wall. Among the significant limitations of the MR method we should mention:

– lack of MR signal from pulmonary air-tissue which is the basis of image construction and therefore small lesions surrounded with pulmonary parenchyma are hardly visible
– artifacts which occur during patient's respiratory movements and the movements of mediastinal organs
– low linear resolution which does not allow a precise definition of morphology of small focal lesions
– long duration of the procedure which results from the necessity to use gating of respiratory and heart movements

The indications for thoracic MR in the first place include the evaluation of pathologic changes within the structures of heart and large mediastinal vessels. In case of proliferative processes the MR enables a more precise (than the CT) evaluation of infiltration to the thoracic wall, mediastinal organs, heart, large vascular trunks and presence of metastases in mediastinal lymphatic glands [34].

Although rarely performed due to small dimensions of H and deep localization, the thin-needle biopsy monitored by RTG, CT or USG is the examination of high specificity, especially if the lesion is situated near the surface of lung or subpleurally. In most cases it provides diagnostic cytological material. Confrontation of its image with clinical and radiological results, in some cases, followed by immunohistochemical identification of fibromyxomatous structures by means of S-100 protein makes enables correct diagnosis. Unfortunately, the diameter of nodule smaller than 2 cm and its stiff consistency connected to cartilaginous and osseous tissues constitute a serious difficulty in obtaining the representative material [35, 36, 37, 38, 39, 40].

Conclusions

1. Pulmonary hamartomas is a lesion most often found fortuitously in patients aged over 40 years, a bit more often in men.
2. Histologically, they are mainly build of cartilaginous tissue (50% of nodules contain no other tissue component), while mixed forms contain fibrous tissue – 40% and adipose tissue – 15%.
3. Hamartomas occur in the peripheral part of lungs, with no predilections to certain areas in lungs and the size of lesion at the time of diagnosis usually (74%) does not exceed 2 cm.
4. CT examinations reveal calcifications in 30 % of lesions, and in 15 % of cases – presence of adipose tissue.
5. Pulmonary hamartoma has morphologic features which enable its detection in RTG or CT, especially when it contains adipose tissue or typical calcifications.

References:

1. Stedman's Medical Dictionary 24th ed., s.v. "Hamartoma".
2. Kojima R, Mizuguchi M, Bessho F et al.: Pulmonary carcinoma associated with hamartoma in a 11-year-old boy. Am J pediatr Hematol Oncol. 1993 Nov; 15(4): 439–42.
3. Palvio D, Egeblad K, Paulsen SM. Atypical lipomatous hamartoma of the lung. Virchow Arch [A] 1985; 405: 253–261.
4. Rossi G, Cavazza A, Valli R et al.: Atypical lipomatous tumour (lipoma-like well-differentiated liposarcoma) arising in a pulmonary hamartoma and clinically presenting with pneumothorax. Lung cancer. 2003 Jan; 39(1); 103–106.
5. Blair TC, McElvein RM.: Hamartoma of the lung: a clinical study of 25 cases. Dis Chest 1963; 44: 17296–302.
6. Kayser K, Donnwald D, Zink S, Kayser G. Small pulmonary lesions – a challenge for thoracic surgery? ScientificWorld Journal. 2001 Dec 15; 1: 906–13.
7. Risch A, Wikman H, Thiel S. et al.: Glutathione-S-transferase M1, M3, T1 and P1 polymorphisms and susceptibility to non-small-cell lung cancer subtypes and hamartomas. Pharmacogenetics. 2001 Dec; 11(9): 757–64.

8. Lillington GA, Caskey CI. Evaluation and management of solitary and multiple pulmonary nodules. Clin Chest Med 1993.
9. Yang C, Zhao H, Yin H. Diagnosis and treatment of pulmonary hamartoma. Zhonghua Jie He He Hu Xi Za Zhi. 1999 Jul; 22(7): 399–400.
10. David O, Beasley MB, Minardi AJ Jr, Malek F, Kovitz KL. Management of endobronchial hamartoma. J La State Med Soc. 2003 Mar-Apr; 155(2): 110–2.
11. Gjevre JA, Myers JL, Prakash UB. Pulmonary hamartomas. Mayo Clin Proc.1996 Jan; 71(1): 14–20.
12. Hansen CP, Holtveg H, Francis D, Rasch L, Bertelsen S. Pulmonary hamartoma. J Thorac Cardiovasc Surg, 1992 Sep; 104(3): 674–8.
13. van den Bosch JM, Wagenaar SS, Corrin B.et al.: Mesenchymoma of the lung (so called hamartoma): a review of 154 parenchymal and endobronchial cases. Thorax. 1987 Oct; 42(10): 790–3.
14. Fudge TL, Ochsner JL, Mills NL. Clinical spectrum of pulmonary hamartomas. Ann Thorac Surg. 1980 Jul; 30(1): 36–9.
15. Kojima R, Mizuguchi M, Bessho F.et al.: Pulmonary carcinoma associated with hamartoma in a 11-year-old boy. Am J pediatr Hematol Oncol. 1993 Nov; 15(4): 439–42.
16. Kleinman J, Zirkin H, Feuchtwanger MM, Hertzanu Y, Walfisch S. Benign hamartoma of the lung presenting as massive hemoptysis. J Surg Oncol. 1986 Sep; 33(1): 38–40.
17. Sharkey RA, Mulloy EM, O'Neill S. Endobronchial hamartoma presenting as massive haemoptysis. Eur Respir J. 1996 Oct; 9(10): 2179–80.
18. Tomashefski JF Jr. Benign endobronchial mesenchymal tumors: Their relationship to parenchymal pulmonary hamartomas. Am J Surg Pathol 1982; 6: 531–540.
19. Carter D, Eggleston JC Tumors of Lower Respiratory Tract. Series 2. Washington DC: Armed Forces Institute of Pathology. 1980: 221–231.
20. Papla B, Malinowski E. Pulmonary fibroleiomyomatous hamartomas: report of two cases. Patol Pol. 1991; 42(4): 128–30.
21. Chadwick SL, Corrin B, Hansell DM, Geddes DM. Fatal haemorrhage from mesenchymal cystic hamartoma of the lung. Eur Respir J 1995; 8: 2182–84.
22. Mark EJ. Mesenchymal cystic hamartoma of the lung. N Eng J Med 1986; 315: 1255–1259.
23. Mushtag M, Ward SP, Hutchinson JT, Mann JS. Multiple cystic pulmonary hamartomas. Thorax 1992; 47: 1076–77.
24. Xu R, Murray M, Jagirdar J, Delgado Y, Melamed J. Placental transmogrification of the lung is a histologic pattern frequently associated with pulmonary fibrochondromatous hamartoma. Arch Pathol Lab Med. 2002 May; 126(5): 562–6.
25. van Slegtenhorst M, de Hoogt R, Hermans C.et al.: Identification of the Tuberous Sclerosis Gene TSC1 on chromosome 9q34. Science,Vol 277, Issue 5327, 805–808, 8 August 1997.
26. Gomez M, Tuberous sclerosis (Raven, New York,1988); Gomez MR, Ann. N.Y. Acad. Sci. 615, 1 (1991).
27. Hunt A, Shepherd C,J. Autism Dev. Disord. 23, 323 (1993).
28. Carney JA. Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney Triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clinic Proc. 1999 Jun; 74(6): 543–52.
29. Erasmus JJ, Connolly JE, McAdams HP, Roggli VL. Solitary pulmonary nodules: Part I. Morphologic evaluation for differentiation of benign and malignant lesions. Radiographics. 2000 Jan-Feb; 20(1): 43–58.
30. Oei TK, Wouters EF, Visser R.et al.: The value of conventional radiography and Computed Tomography (CT) in diagnosis of pulmonary hamartoma. Roetgenblatter. 1983 Oct; 36(10): 324–7.
31. Siegelman SS, Khouri NF et al.: Pulmonary hamartoma: CT findings. Radiology, Vol 160, 313–317.
32. Swensen SJ, Viggiano RW, Midthun DE et al.: Lung nodule enhancement at CT: multicenter study1. Radiology 2000 Jan 214(1): 73–80.
33. Yungao Ding, Jerold Wallis: Diagnosis: Lung cancer and pulmonary hamartoma http://gamma.wustl.edu/pt037te163.html (accessed 10.02.2005).
34. McLoud TC: Thoracic Radiology the requisites. Mosby1998.
35. Azua Blanco J, Azua Romeo J, Ortego J, Perez Cacho MJ. Cytologic features of pulmonary hamartoma. Report of a case diagnosed by fine needle aspiration cytology. Acta Cytol. 2001 Mar-Apr; 45 (2): 267–70.
36. Dunbar F, Leiman G. The aspiration cytology of pulmonary hamartomas. Diagn Cytopathol. 1989; 5(2): 174–80.
37. Ramzy I. Pulmonary hamartomas: cytologic appearances of fine needle aspiration biopsy. Acta Cytol. 1976 Jan-Feb; 20 (1): 15–9.
38. Torkian B, Kanthan R, Burbridge B. Diagnostic pitfalls in fine needle aspiration of solitary pulmonary nodules. Two cases with radio-cyto-histological correlation. BMC Pulm Med. 2003; 3: 2.
39. Hummel P, Cangiarella JF, Cohen JM, Yang G, Waisman J, Chieng DC. Transthoracic f fine-needle aspiration biopsy of pulmonary spindle cell and mesenchymal lesions: a study of 61 cases. Cancer 2001 Jun 25; 93 (3): 187–98.
40. Wiatrowska BA, Yazdi HM, Matzinger FR, MacDonald LL. Fine needle aspiration biopsy of pulmonary hamartomas. Radiologic, cytologic and immunocytochemical study of 15 cases. Acta Cytol. 1995 Nov-Dec; 39(6): 1167–74.