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Pulmonary hamartoma: a clinic-pathologic study of 206 consecutive cases focusing on different histologic variants

Laura Melocchi[1], Alberto Cavazza[2], Maria Sirolli[3,4], Elisa Albertini[3,4], Sofia Melotti[3,4], Tommaso Bizzarro[5], Arianna Oberti[1,6], Fabio Davoli[7,8], Giulio Rossi[1]

Contributions: (I) Conception and design: L Melocchi, G Rossi; (II) Administrative support: G Rossi, A Cavazza; (III) Provision of study materials or patients: G Rossi, A Cavazza, F Davoli; (IV) Collection and assembly of data: L Melocchi, G Rossi, F Davoli, T Bizzarro; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

【**Abstract**】 **Background:** Pulmonary hamartoma (PH) is the most common benign pulmonary tumor usually presenting as a solitary, well-demarcated nodule composed of mature cartilage and adipose tissue. Some unusual histologic variants are challenging on clinic-radiologic and pathologic examination. **Methods:** We collected a multicentric, retrospective, consecutive series of 206 PH with clinical characteristics and histologic variants. **Results:** Clinical data were in line with the literature demonstrating a male prevalence (2:1) and a median age of 61.6 years. The median size of the nodule was 17.8 mm. When performed, SUVmax >2.5 at FDC-PET was evidenced in 4% of cases (5 out of 119) and was significantly associated with undifferentiated/myxoid histology. Conventional histology showing chondroid or chondro-lipomatous PH was quoted in 186 cases (90%), while leiomyomatous and undifferentiated/myxoid variants were recorded in 20 cases (10%). The high rate of unusual variants on pathology is possibly related to a selection bias due to external consultations or surgical excision of the lesions lacking classic features at imaging studies. **Conclusions:** About 10% of PH may show unusual histology and SUVmax >2.5 at FDC-PET in 4%. These uncommon findings may challenge the correct recognition, raising some concerns in terms of differential diagnosis with several other mesenchymal tumors in the lung. These features should be kept in mind to achieve a correct diagnosis and avoid unnecessary invasive treatments.

【**Key words**】 Hamartoma; lung; WHO; histology; immunohistochemistry; incidence; imaging

Introduction

Pulmonary hamartoma (PH) is a relatively common lesion with which pathologists dealt during routine practice and frozen section, representing the most common benign tumor of the lung[1-5]. In the general population, the incidence of PH is about 0.25% with a male-to-female ratio of 2:1–4:1 and a median age of 60 years[1-5]. PH usually represents an asymptomatic and incidental lesion during imaging studies for other reasons and radiologically appears as a peripheral nodule with rounded margins consisting of a combination of mature mesenchymal tissues, mainly cartilage and fat

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[1]Pathology Unit, Department of Oncology, Fondazione Poliambulanza Hospital Institute, Brescia, Italy; [2]Pathology Unit, Azienda USL/IRCCS di Reggio Emilia, Reggio Emilia, Italy; [3]Pathology Unit, Santa Maria delle Croci Teaching Hospital, Azienda USL of Romagna, Ravenna, Italy; [4]Resident of the School of Specialization in Anatomic Pathology "A.M. Mancini", University of Bologna, Bologna, Italy; [5]Operative Unit of Pathologic Anatomy, Azienda USL of Romagna, Infermi Hospital, Rimini, Italy; [6]Specialty School of Pathologic Anatomy, University of Brescia, Brescia, Italy; [7]General and Thoracic Surgery Unit, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy; [8]Department of Thoracic Surgery, Azienda USL of Romagna, Santa Maria delle Croci Teaching Hospital, Ravenna, Italy

Corresponding author: Giulio Rossi, MD, PhD. Pathology Unit, Department of Oncology, Fondazione Poliambulanza, Via Bissolati, 57 - 25124 – Brescia, Italy. Email: giurossi68@gmail.com.

with "popcorn"-like calcification[4-5]. Nevertheless, PH may show myxoid and/or undifferentiated mesenchymal tissue with a prominent entrapped epithelial component raising some concerns about its correct recognition[3,5-7]. In addition, although the argument is still controversial, malignant change have been reported in PH[8-10]. A consecutive series of 206 PH from different institutions is here analysed, focusing on the incidence of histologic variants and their relationship with clinic-radiologic findings. We present the following article in accordance with the STROBE reporting checklist (available at https://www.thecjts.cn/article/view/10.3877/cma.j.issn.2095-8773.2022.03.01/rc).

Methods

Two-hundred six cases of surgically-resected PH were collected from January 2007 to December 2021 from the archival files of the Pathology Units of the Santa Maria delle Croci Hospital of Ravenna, Infermi Hospital of Rimini, Azienda USL/IRCCS di Reggio Emilia and the consultation files of the authors. The specimens were fixed in 10% buffered formalin and then paraffin-embedded in blocks after gross examination.

The most relevant clinic-pathologic and radiologic features of this series are reported in *Table 1*. All the cases consisted of a surgically-resected specimen. Relevant clinical and imaging data were obtained in each case from medical records and/or referring clinicians and pathologists. All the available haematoxylin-eosin-stained slides (range, 2–11; mean 4.5) were reviewed. When appropriate, immunohistochemical stains were performed using an automated immunostainer (Benchmark, Ventana, Tucson, AZ, USA) and the following primary antibodies: pan-cytokeratin (clone AE1/AE3 and MNF116), CK8/18/19 (clone CAM5.2), TTF-1 (clone 8G7G3/1), EMA (clone E29), CK7 (clone SP52), p40 (clone BC28), CK20 (clone, SP33), MUC 2 (clone MRQ18), MUC5AC (clone MRQ19), HNF4alfa (clone EPR16885, Abcam, Cambridge, UK), CDX2 (clone, EPR2764Y), napsin A (clone, MRQ60), desmin (clone D33), smooth-muscle actin (clone, 1A4).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethical committee of the Azienda Unità Sanitaria Locale (AUSL)-IRCCS of Reggio Emilia (No. 14790) and informed consent was taken from all the living patients. For all deceased patients, permit were obtained from the Privacy Authority. All information regarding the human material was managed using anonymous numerical codes.

Table 1 Summary of clinicopathological features of pulmonary hamartoma

Features	Pulmonary hamartoma (n=206)
Sex, n (%)	
Male	136 (66)
Female	70 (34)
Age (years), mean (range)	61.6 (46–81)
Size (mm), mean (range)	17.8 (8–55)
Site, n (%)	
Right upper lobe	51 (25)
Right middle lobe	4 (2)
Right lower lobe	63 (30)
Left upper lobe	43 (21)
Left lower lobe	45 (22)
Slides number per case, mean (range)	2.5 (2–8)
Intraoperative examination, n (%)	37 (18)
Hamartoma	32 (86.5)
Deferred	5 (13.5)
Other	–
Histology	
Chondroid/lipomatous	129 (62.3)
Chondroid	57 (27.7)
Myxoid	12 (6)
Leiomyomatous	8 (4)
Multifocality	–
Surgical procedure, n (%)	
Wedge resection	68 (33)
Enucleation	130 (63)
Segmentectomy	7 (3.5)
Lobectomy	1 (0.5)
PET with 2-deoxy-2-[fluorine-18] fluoro-D-glucose, n (%)	119/206 (58)
SUVmax index, n (%)	
<2.5	114/119 (96)
>2.5	5/119 (4)

PET, Positron emission tomography; SUVmax, maximum standardized uptake value.

Statistical analysis

Statistical calculations with comparison of categorical variables were performed using the chi-square statistic with the Fisher exact test P values.

Results

The series consisted of 206 consecutive and surgically-resected PH with male-to-female ratio of about 2:1 (136 males and 70 females) and median age of 61.6 years (range, 46–81 years).

The median size of the nodules was 17.8 mm, with a wide range between 8–55 mm (*Figure 1*). The lesions were almost equally distributed in right (118 cases, 57%) and left (88 cases, 43%) lungs.

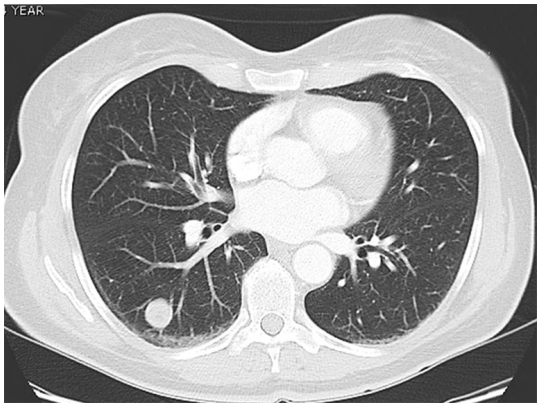

Figure 1 A Leiomyomatous pulmonary hamartoma of the right lower lobe at comuted tumography. The lesion consists of a peripheral, well-defined nodule lacking calcification or fat density.

One-hundred thirty cases (63%) underwent surgical enucleation, while 68 had wedge resection, 7 and 1 cases were excised by segmentectomy and 1 lobectomy, respectively.

Fluorodeoxyglucose positron-emission tomography (FDC-PET) was performed in 119 cases with a SUV max <2.5 in 114 cases (96%), while 5 cases had a SUV max >2.5 (4%).

At histology, 62.3% (129 cases) showed a variable mixture of chondroid and lipomatous tissue (*Figure 2*), while 57 cases (27.7%) entirely consisted of chondroid tissue, 12 cases (6%) showed an undifferentiated mesenchymal tissue with myxoid changes (*Figure 3*) and 4% (8 cases) consisted of bland smooth muscle tissue (*Figure 4*). Of note, as previously observed (7), mucinous gland proliferation was disclosed only in leiomyomatous PH (5 out of 8). No cases of multifocality neither malignant transformation was observed.

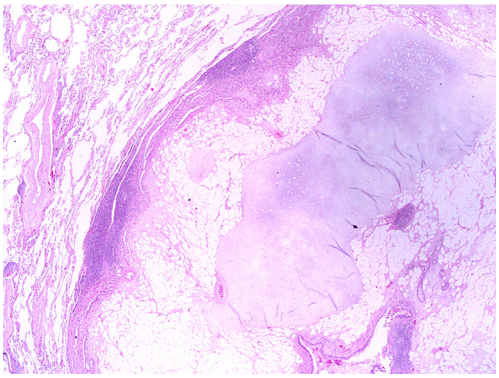

Figure 2 A conventional pulmonary hamartoma predominantly consisting of regular chondroid and adipose tissue centrally entrapping a bronchiolar structure (haematoxylin-eosin stain, ×125).

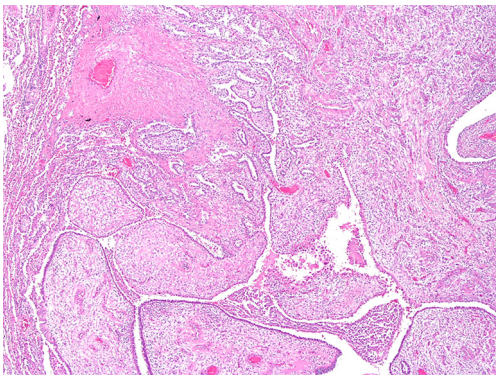

Figure 3 A pulmonary hamartoma consisting of undifferentiated mesenchymal tissue entrapping alveolar structures and forming papillary-like formations (haematoxylin-eosin stain, ×100).

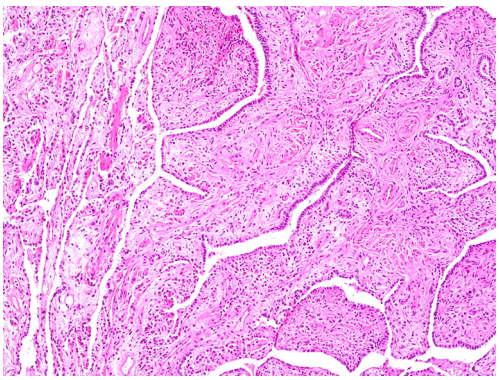

Figure 4 A leiomyomatous pulmonary hamartoma showing a benign smooth muscle proliferation entrapping alveolar structures and creating papillary-like formations (haematoxylin-eosin stain, ×200).

At statistical analysis, no significant differences were observed between clinical characteristics (age, gender) and pathologic features (histology, tumor size, SUVmax). Of note, a statistically significant correlation was noted between histology and SUVmax, since only PH with undifferentiated/myxoid tissue showed a SUVmax >2.5 (P<0.001).

Discussion

PH is the most common primary benign tumor of the lung and generally represents an incidental finding during imaging studies for other reasons[1-5]. Imaging features at computed tomography consisting of a smooth-slightly lobulated, peripheral solitary nodule with popcorn-like calcifications and fatty density are entirely diagnostic of PH[11]. At histology, PH generally contains a mixture of soft tissues, including cartilage, fat, smooth muscle, fibromyxoid tissue, bone, undifferentiated mesenchyme and less frequently smooth muscle growing in the interstitium and entrapping regular bronchioli and/or alveoli with hyperplastic pneumocytes, even leading to papillary formations at the periphery of the nodule[3,5].

However, PH may show unusual features either at imaging (giant and cystic appearance, multifocality) and histologic (prominent alveolar entrapment and papillary formations, smooth muscle or undifferentiated mesenchymal tissue) grounds raising some concerns about a correct diagnosis[3,5,12,13].

A recent retrospective study by Chatzopoulos *et al.*[14] on 979 PH revealed that 0.6% were multiple, 0.4% located akin to lung adenocarcinoma and 0.2% appeared as mediastinal masses. However, none of these occurrences were observed in our series.

In the seminal study by Gjevre *et al.*[2] on 215 patients, a male prevalence (2:1 ration) and a peak incidence in the seventh decade was observed. No recurrence neither malignant change has been reported. Despite 29% had a concurrent tumor (lung cancer in 33 out of 39 cases), the authors did not demonstrate a related pathogenesis between hamartoma and synchronous tumors. The clinic-pathologic characteristics in our series overlap the aforementioned with a male predominance (66% *vs.* 34%), a median age of 61.6 years and no evidence of malignant changes. However, 5 peculiar cases among this series have been previously published as mucinous adenomyomatous PH in light of the unusual histologic association of smooth muscle component and a prominent mucinous gland proliferation at the periphery[7]. Even in the current consecutive series, the only PH with an entrapped epithelial mucinous growth showed a unique leiomyomatous mesenchymal component. Nevertheless, we failed to disclosed overt malignancy in PH in agreement with other studies[15-17].

Hamartomas usually do not take up fluorodeoxyglucose avidly on positron-emission tomography CT. In a retrospective study of 87 peripheral PH by Uhlén *et al.*[18] the mean ^{18}F-FDG PET/CT SUVmax of PH was significantly lower than that observed in carcinoids (1.4 *vs.* 3.9).

An interesting finding emerging from our series is the statistically significant association between PH with undifferentiated/myxoid component and a SUVmax >2.5, while more conventional PH had a low glucose uptake. In addition, 4 out of 5 deferred diagnoses of PH at intraoperative examination consisted of PH with undifferentiated/myxoid mesenchymal component.

Frozen sections on PH does not represent an infrequent event in routine practice, generally resulting in a correct diagnosis. No misdiagnosis was made among benign solitary nodules in the study by Marchevsky *et al.*[19] including 10 PH. In the current study, intraoperative examination was requested in 37 out of 206 PH (18%). A definitive correct diagnosis was performed on frozen sections in 32 cases (86.5%), while 5 cases (including 4 PH with undifferentiated/myxoid and 1 leiomyomatous PH) were initially reported as possibly benign uncertain mesenchymal lesions and then deferred on formalin-fixed and paraffin-embedded definitive slides.

The differential diagnosis mainly depends on the type of soft tissue represented and the degree of entrapped respiratory epithelium, but does not pose difficulties in presence of at least two different types of mesenchymal tissue such as cartilage, adipose and/or myxoid component with/without entrapped respiratory epithelium[3,5] (*Table 2*). However, chondroma, adenofibroma, intrapulmonary solitary fibrous tumor, inflammatory myofibroblastic tumor, and benign metastasizing leiomyoma should be variably considered.

Sporadic chondroma is very uncommon, while it commonly arises in patients with Carney triad (i.e., gastrointestinal stromal tumors, pulmonary chondromas, paragangliomas)[5]. Absence of entrapped epithelium, presence of bone metaplasia with calcification and a fibrous pseudocapsule are typical features of chondroma. Loss of succinate dehydrogenase-B (SDHB) at

immunohistochemistry is a useful finding in Carney-associated chondromas[20]. Pulmonary lipoma generally shows an endobronchial rather than a peripheral location, but it shares identical HMGA2 gene translocation and the distinction from hamartoma may be very arbitrary.

Entrapped epithelial cells in PH generally consists of cleft-like spaces lined by hyperplastic, monomorphic, cuboidal type 2 pneumocytes without nuclear atypia or ciliated respiratory epithelium. However, the presence of prominent alveolar/bronchiolar entrapment with formations of pseudo-papillary projections may pose some problems in differential diagnosis with adenofibroma. Pulmonary adenofibroma (PAF) is an unusual, well-circumscribed benign tumor of unknown histogenesis characterized by leaf-like formations lined by bland-looking cuboidal or columnar respiratory epithelium and dense sclerosing, acellular stroma peripherally entrapping alveolar structures[21]. No specific primary antibodies or genetic alterations were described so far. The finding of hyaline cartilage, fibrous tissue, smooth muscle and/or adipocytic components clearly favors PH.

Table 2 A concise summary of the clinic-pathologic helpful features of tumor in differential diagnosis with pulmonary hamartoma

Tumor type	Gender	Specific clinical features	Morphology	Ancillary techniques
Hamartoma	Male > female	Peripheral > endobronchial		HMGA2-LPP fusion gene due to the translocation t(3;12)(q27-q28; q14-q15), consisting of exons 1–3 of HMGA2 and exons 9–11 of LPP. HMGA2 is consistently expressed in hamartoma and lipoma
Chondroma	Females in Carney's triad; male prevalence in sporadic form	Multiple nodules in Carney's triad; peripheral (very rare endobronchial site)	Well-circumscribed nodule with fibrous pseudocapsule, hyaline cartilage with/without bone metaplasia and/or calcification; lack of entrapped epithelium	SDHB deficiency and expression
Adenofibroma	Female > male	Peripheral	Leaf-like projections lined by cuboidal/columnar epithelium and acellular, sclerotic stroma with/without calcifications and alveolar entrapping	No specific markers
Intrapulmonary solitary fibrous tumor	No predilection	Peripheral	Tumor growth of spindle cells generally alternating hypo-and hypercellularity in various areas of the lesion	STAT6 (product of *NAB2-STAT6* gene fusion) and CD34 expression
Benign metastasizing leiomyoma	Female	Past or current history of uterine leiomyomas; peripheral nodule/s	Solid proliferation of smooth muscle spindle cells lacking significant atypia or mitotic rate entrapping alveolar structures at the periphery	Expression of smooth muscle markers, hormonal receptors
Inflammatory myofibroblastic tumor	No predilection	More frequent in childhood	Ill-defined proliferation of spindled myofibroblasts with/without ganglion-like cells intermingled with inflammatory infiltrate (plasma cells, lymphocytes and eosinophils), also entrapping alveoli with hyperplastic pneumocytes	Expression of smooth muscle markers. ALK1 expression in a subset with *ALK1* gene rearrangement. Increase of IgG4 positive plasma cells in myofibroblastic proliferation secondary to IgG4 syndrome

Solitary fibrous tumor (SFT) is generally a pleura-based mesenchymal tumor with different grade of malignancy expressing CD34 and STAT6 (the product of the *NAB2-STAT6* gene fusion), but rarely presenting as an intrapulmonary form[22]. Alveolar entrapping may be prominent leading to pseudopapillary formations[23].

Inflammatory myofibroblastic tumor consists of a spindle cell proliferation expressing smooth-muscle markers and with ALK in half of cases. The tumor cells are closely intermingled with a variable number of inflammatory cells sometimes showing a myxoid background[3,5]. Pulmonary benign metastasizing leiomyoma is a rare occurrence secondary to lung spread of uterine leiomyomas predominantly found in premenopausal women[24]. The lesion consists of single or multiple nodular proliferation of bland-looking smooth muscle entrapping alveoli and expressing estrogen/progesterone receptors at immunohistochemistry. The history of uterine leiomyomas is the clue in suggesting this diagnosis.

Although the series here includes a consecutive number of PH, some limitations of the study are related to the retrospective design and particularly to the high rate of unusual cases, namely leiomyomatous and undifferentiated/myxoid PH, due to some selection bias from consultation cases and the non-interventional behaviour of clinicians in PH likely recognized on classic CT scan features, as suggested in a recent meta-analysis[16].

In conclusion, we reported a consecutive and multicentric series of 206 PH with various histologic features, confirming the benign clinical behavior and the lack of malignant transformation in PH. Nevertheless, some unusual histologic features, in particular PH with undifferentiated/myxoid and leiomyomatous component, may show an increased glucose uptake and pose diagnostic problems when frozen section examination is required. Physicians and pathologists should be aware of these uncommon presentations to avoid unnecessary invasive treatments.

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