Multiple sclerosing pneumocytomas: a review

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ABSTRACT

Sclerosing pneumocytoma (SP) is a rare benign low-grade tumour of the lung, and typically presents as single discrete coin lesions on imaging. Multiple SP is an exceedingly rare entity and thus reported sparingly. We review the literature on multiple SP, their clinical presentations, histopathology, relevant differential diagnoses and molecular histogenesis of this entity. SP has a predilection for East Asian origin females who have never smoked. Patients are either asymptomatic or have symptoms such as cough, haemoptysis that may be persistent, chest pain if involving the pleura and presents as discrete coin lesion on chest X-ray. Histologically, they are papillary, solid, angiomatoid or sclerotic, or combinations of these four basic patterns. Multiple lesions have the same or slightly different histological patterns. They can be distributed in either lung, in any lobe and can even be bilateral. *AKT-1* molecular pathways are pivotal in their molecular pathogenesis. In this review, we further propose a classification based on five types of distribution of multiple SP.

INTRODUCTION

Sclerosing pneumocytoma (SP) is a somewhat enigmatic primary, benign lung tumour that was first described in 1956 under the appellation, 'sclerosing haemangioma'.[1]

Due to the presence of blood and spaces that are filled by blood, these lesions were initially thought to be sclerosing variants of haemangiomas. It is now known they are epithelial neoplasms. Solitary SP is encountered occasionally in routine practice, which typically present as a solitary, peripheral lung lesion on surgical resection. Multiple SPs, on the other hand, are exceedingly rare, but low-grade tumours; they have a striking female-predominant distribution and seen especially in East Asian ancestry. This entity, while benign, nonetheless can pose significant concern and diagnostic challenges both from clinical and pathology standpoints. Careful review of the histology of these lesions, with particular attention to it's cellular components, immunohistochemical profiling and clinicopathological correlation are key steps in ensuring an accurate diagnosis and subsequent management of multiple SPs. Awareness that multiple SPs exist, their unique distribution patterns, differential diagnosis, immunohistochemical features and molecular pathogenesis form the basis of this review.

CLINICAL PRESENTATION

In the seminal series described by Liebow and Hubbell, patients were either asymptomatic or presented with cough, haemoptysis that sometimes may be persistent, chest pain if pleural based or involving the pleura, and a discrete coin lesion on chest X-ray.[1] SP has a distinct predilection for middle-aged never-smoking females of East-Asian ancestry.[2–4]

In the largest series of SP (n=100 cases), only four were found to be multiple.[3] Despite its rarity, however, multiple SPs have been documented in the literature.[3 5–7]

All reported cases of multiple SP share similar striking female-predominant distribution (see table 1). The typical age at presentation ranges from 16 to 73 years (mean: 40.6 years). The patients reported in the literature are either asymptomatic or present with non-specific symptoms such as haemoptysis and cough.

NUMBER, SIZE AND DISTRIBUTION OF MULTIPLE SP

As can be seen in table 1, in several of the reported cases, the exact number of SP lesions is often not mentioned but merely recorded as 'multiple'. The number of multiple SPs that are documented range from 2 to 7 in a single patient. In reported multiple SP cases, the mean is 3.6 SP lesions per patient. Typical size of these lesions ranged from 1.2 cm to a high of 5.0 cm in greatest dimension (mean size: 3.0 cm).

SPs are encountered in all lobes of both lungs. In an effort to bring a degree of order, we performed a classification scheme based on the distribution and location of multiple SPs reported in the literature and two cases from our surgical pathology archives into various types (figure 1). The proposed classification is as follows: (1) type I: a dominant SP with satellite nodules that occur in one lobe (multifocal); (2) type II: SPs that are discrete, separate lesions in the same lobe; (3) type III: SP occurring in different ipsilateral lobes; (4) type IV: SP occurring in

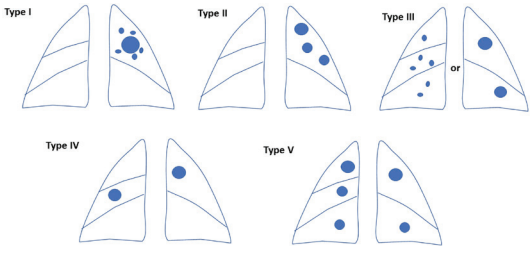

Figure 1 The various subtypes of multiple SP. Type I: a dominant SP with satellite nodules that occur in one lobe (multifocal). Type II: SPs that are discrete, separate lesions in the same lobe. Type III: SP occurring in different ipsilateral lobes. Type IV: SP occurring in different contralateral lobes. Type V: SP occurring bilaterally in all lobes. SP, sclerosing pneumocytoma.

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Table 1 Literature review of multiple SP cases

Reference	Age/gender	Symptoms	No	Maximum size cm	Pattern	Site
6	NA	NA	2	1.2; 5.0	Type I	NA
9	40/F	Haemoptysis	Multiple	5.0	Type I	R upper lobe
12	48/F	Haemoptysis	Multiple	3.7	Type I	R lower lobe
13	48/F	NA	4	5.0	Type IV	L lower lobe, lingula, R middle lobe
3	NA	NA	3	3.0	Type I and II	NA
14	38/F	NA	Multiple	3.1	Type III	All lobes R lung
8	16/F	NA	Multiple	5.0	Type V	All lobes both lungs
15	73/F	NA	3	NA	Type IV	R and L lower lobes
16	25/F	NA	Multiple	NA	Type IV	R and L lungs
17	19/F	Asymptomatic	7	1.8	Type I	R middle lobe
5	31/F	NA	Multiple	2.5	Type III	R upper, middle and lower lobes
Our records	53/F	Asymptomatic	2	2.3	Type III	L upper and lower lobes
Our records	56/F	Asymptomatic	4	1.8	Type IV	L upper lobe,lingula, R middle and lower lobe

F, female; L, left; NA, not applicable; R, right.

different contralateral lobes and (5) Type V: SP occurring bilaterally in all lobes.

When looking at our own series, we encountered two asymptomatic females who had two and four SP lesions, involving the left upper and lower lobes (type III) and in the lingula, left upper, right middle and lower lobes (type IV), respectively. Table 1 displays the distribution of reported cases based on the above classification. Indeed all five types are encountered with type I (five cases) being the most common and type V being the rarest scenario, only described in two cases so far.[8 9]

RADIOLOGY

Radiological examinations typically include routine chest X-ray, MRI and CT scans (figure 2). The classic case of SP appears as peripheral well-defined, discrete and solitary nodular lesion/s that reveal as oval to rounded non-infiltrative shadows on chest X-ray. They occasionally contain areas of calcification and may show an air-meniscus sign: crescentic radiolucency at the periphery of a lung nodule.

On CT scans, they are visualised as well-defined, intraparenchymal nodular masses often subjacent to the pleura with inhomogeneous enhancement. Similar to the chest X-ray, CT can also detect areas of calcification and a radiolucent zone around the lesion.

TREATMENT

The lesions are usually treated by surgical enucleation and/or a simple wedge resection.

GROSS APPEARANCE

The vast majority of multiple SP tend to be about 1–2 cm in diameter (while rare lesions can be larger as depicted in table 1), are well circumscribed being delineated peripherally by compressed lung. The cut surface ranges from grey to red, or reddish-brown, and sometimes they may be calcified or necrotic.

MICROSCOPIC APPEARANCE

The principal histological patterns that are encountered in multiple SP are the same as solitary SP: papillary, solid, angiomatoid or sclerotic, or combinations of these four patterns.[3 4 6] Combinations of these various patterns may be encountered in the different SP lesions in multiple SP cases. In other words, the

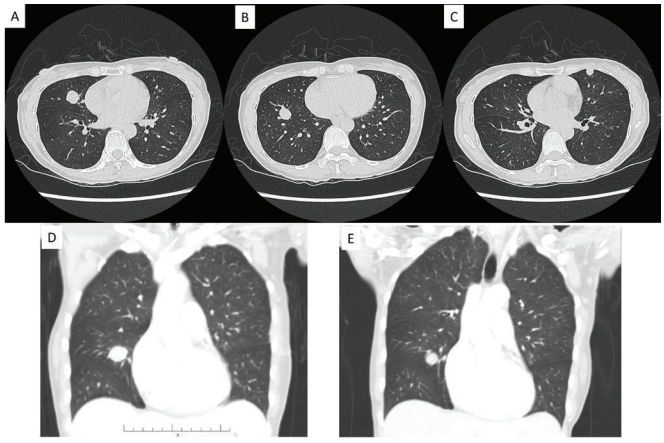

Figure 2 A CT scan demonstrates three bilateral lung nodules, in right middle (A) and lower lobes (B) and in left upper lobe (C). Ensuing CT scans highlights almost minimal interval change of right middle (D), and lower lobe lung nodules (E).

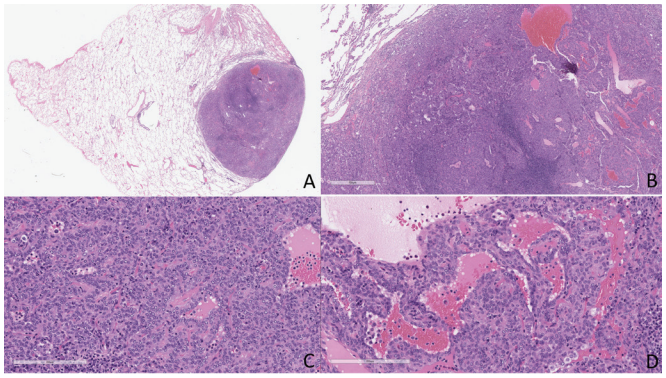

Figure 3 Low-power magnification shows a discrete and well-circumscribed cellular tumour nodule in lung periphery (A). Higher power magnification demonstrates diffuse proliferation often with ectatic vascular spaces (B–D) filled with red blood cells (B, D). Cuboidal surface cells lines these ectatic vascular spaces. A distinct round cell population (central bland nuclei and eosinophilic cytoplasm) forms intervening solid areas (C). Occasional foamy histiocytes and small aggregates of lymphocytes are often admixed with this tumour (B–D).

multiple SPs, all the lesions do not necessarily have the same histological pattern.

SP lesion is well-circumscribed nodule (figure 3A). Within the cellular lesion cuboidal surface cells form vague papillary structures, often lining ectatic vascular spaces (figure 3B–D). The cuboidal surface cells demonstrate small round nuclei with vesicular chromatin, inconspicuous to small nucleoli, and small amount of pale vacuolated cytoplasm. The second round cell population forms the solid areas of this tumour (figure 3C,D). These round cells demonstrate small, round to oval slightly irregular nuclei with occasional grooves, vesicular chromatin, small nucleoli and inconspicuous eosinophilic cytoplasm. Occasional admixture of small lymphocytes and foamy macrophages can be seen.

IMMUNOHISTOCHEMISTRY

By immunohistochemistry, the surface cuboidal cells are positive for pancytokeratin (AE1/AE3), CK7 and epithelial membrane antigen (EMA), whereas the round cells show only patchy expression for EMA and AE1/AE (focal) (figure 4A–C). There is diffuse vimentin expression in both cellular compartments (figure 4D). Both cuboidal and round cell populations show strong/diffuse expression for thyroid transcription factor-1 (figure 4E) and, weak multifocal/patchy expression of progesterone receptor (figure 4F). Cytoplasmic and membrane expression for MIB-1 (rather than the usual nuclear staining) has been used in diagnostic workup of SP; however, some of the discrepant result is likely a clone-dependent phenomenon.[10]

HISTOGENESIS

Through multiple studies, it is now clear that the histogenesis of the lesion is epithelial and the cell of origin is type II pneumocytes.[3 4]

DIFFERENTIAL DIAGNOSIS

Given SP displays varied histopathological patterns, the differential diagnosis that one entertains depends largely on the dominant pattern and is consequently wide (table 2). This, therefore, ranges from non-tumour conditions to both benign and malignant tumours. Non-tumour conditions include pulmonary infarction, scar tissue, reparative or reactive changes following inflammation (from any cause), atypical adenomatous hyperplasia, radiation or even drugs that can result in florid type II pneumocyte hyperplasia. Benign tumour/lesions of the lung that may mimic SP are sugar tumour (PEComa), pulmonary hamartomas, alveolar adenoma and a true haemangioma. As for malignant tumours, lung adenocarcinoma (lepidic and especially papillary predominant adenocarcinoma) as well as poorly differentiated non-small cell carcinoma (especially in biopsy setting) must be distinguished from SP. Among other malignancies,

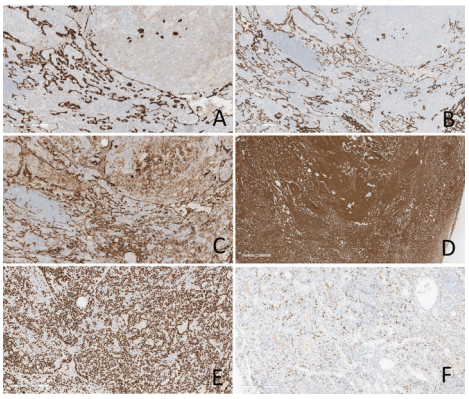

Figure 4 Immunohistochemical findings show the round cell component showed only weak/focal expression for AE1/AE3 (A) while surface cuboidal cells were positive for both AE1/AE3 (A) and CK7 (B). EMA was positive in both surface cuboidal cells (strong) and round cells (weak to moderate) and showed moderate EMA expression (C). Both cell population were positive for vimentin (D) and diffusely expressed TTF-1 (E). Progesterone receptor expression was present in only a subset of round cells (F). EMA, epithelial membrane antigen; TTF-1, thyroid transcription factor-1.

Table 2 Differential diagnosis of sclerosing pneumocytoma (SP)

Diagnosis	Histology	Immunohistochemistry
Sclerosing pneumocytoma	Two cells: surface epithelial cells that resemble type II pneumocytes, and round stromal cells arranged in four patterns: papillary, sclerosing, solid,and haemorrhagic	Surface epithelial cells:+ve for thyroid transcription factor-1 (TTF-1), napsin A, cytokeratin; round stromal cells:+ve TTF-1; –ve for napsin A, cytokeratin
Organising phase diffuse alveolar damage	Typically diffuse (no mass lesions). No round cell component.	
Reactive conditions (atypical adenomatous hyperplasia—AAH, infarction, scar)	AAH typically small lesion and composed purely of type II pneumocytes. Fibrosis, haemorrhage, scarring and absence of the stromal round cells and biphenotypic histology of SP	Reactive pneumocytes+ve for TTF-1, cytokeratin; No TTF-1 +ve stromal cells
Alveolar adenoma	Especially solid variant can be difficult on morphology. No round cell population	No TTF-1 +ve stromal round cells
Sugar tumour (PEComa)	Cords and rounded nests of glycogen-rich cells with clear to eosinophilic granular cytoplasm well-defined cell borders with delicate sinusoidal vasculature	Cells+ve for: HMB45, Melan A, MITF, SMA, desmin and variably for S100 Cells –ve for: cytokeratin
Hamartoma	Presence of bronchial epithelium, mature cartilage and smooth muscle	Unremarkable
True haemangioma	True vascular spaces filled with blood and lined with endothelial cells, no stromal component	Endothelial cells+ve for: ERG, CD31, CD34 Cytokeratin –ve
Adenocarcinoma	Can be papillary lacks the two-cell pattern of surface pneumocytes and round stromal cells, has more cytological atypia, mitoses	Cells+ve for: TTF-1 and pan-cytokeratin
Carcinoid tumour	Uniform cells in nests, trabeculae, eosinophilic cytoplasm, rosette formation, salt and pepper chromatin	Cells+ve for: synaptophysin, chromogranin, diffuse cytokeratin
Poorly differentiated NSCLC	Sheets of tumour cells, cytological atypia, mitoses, necrosis	Cells+ve for: TTF-1, napsin A, cytokeratin No TTF-1 +ve stromal cells
Metastatic undifferentiated carcinoma	Sheets of pleomorphic cells, cytological atypia, frequent mitoses and necrosis	Cells+ve for: cytokeratins Cells –ve for: TTF-1, napsin A
Solitary fibrous tumour	Especially cellular variant with ectatic vessels. Absence of round cell population	Neoplastic cells+for CD34, STAT6; negative for cytokeratin and TTF-1
Epithelioid haemangioendothelioma	Cellular and solid variant. Myxohyaline stroma and lack of round cell population	Neoplastic cells+for ERG; negative for cytokeratin and TTF-1
Melanoma	Epithelioid or spindle cells, prominent nucleoli, eosinophilic cytoplasm, rhabdoid cells, may have melanin, packaged	Cells+ve for: S100, HMB45, melanoma cocktail, SOX10 Cells –ve for: TTF-1, napsin A, cytokeratins

NSCLC, non small cell lung carcinoma; -ve, negative; +ve, positive.

carcinoid (neuroendocrine) tumour, metastatic carcinomas and melanomas potentially may mimic SP to a greater or lesser degree.

MOLECULAR PATHOGENESIS

While the cell of origin of SP was the original preoccupation of pathologists, more recently several have turned their attention to its molecular pathogenesis. Early loss of heterozygosity (LOH) studies showed a striking similarity to bronchiolar alveolar carcinoma: LOH at 5q and 10q, as well as LOH at the p16 locus.[2 7 11] More recently, Jung *et al* undertook a deep whole-exome sequencing of 44 SP and found that 45.6% of cases harboured recurrent somatic mutations (or copy number alterations) in *AKT1* and a further 4.5% displayed *β-catenin* mutations.[11] These results were recapitulated by Fan *et al* whose whole-exome sequencing of a case of SP implicated the following pathways in the molecular pathogenesis of SP: P13K/AKT and VEGF signalling pathways with *AKT1* being pivotal.[5] One of the key and perhaps reassuring observations from the SP genome profiling studies is that they were all negative for the classic driver mutations of lung adenocarcinoma (*EGFR*, *KRAS*, other lung adenocarcinoma specific driver mutations, *ALK* or *ROS1* fusions).

Take home messages

- Sclerosing pneumocytoma is an uncommon, most often solitary primary pulmonary neoplasm.
- Multiple tumours are extremely rare and are mistaken radiologically for metastasis.
- There is a distinct predilection for females of East Asian origin.
- Multiple lesions may be in the same lobe, different lobes or multiple lobes on one or both lungs.
- *AKT-1* gene pathways are pivotal in the pathogenesis.

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