Leading Article

Primary pulmonary sarcomatous and mixed epithelial-mesenchymal neoplasms

Michael A. den Bakker¹ and Robert-Jan van Suylen²

¹Department of Pathology, Maasstad Hospital, Rotterdam, The Netherlands and ² Department of Pathology, DNA, Jeroen Bosch Ziekenhuis, den Bosch, The Netherlands

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Introduction

The vast majority of primary pulmonary neoplasms arise from the epithelial cells of the airway conductive system. The high proportion of epithelial neoplasms in the lung is easily explained by the large surface area of the lung and the continued renewal of its epithelial lining and the exposure to carcinogens. In contrast, the supporting tissues only make up a small fraction of the lung parenchyma and their renewal turnover is low. This is especially relevant in the interstitial alveolar tissue of the gas-exchange compartment where the amount of connective tissue is minimal. Thus, primary mesenchymal tumours in the lung are very rare and most commonly arise in the larger airways. Most tumours with morphological mesenchymal phenotype (pure or mixed) are likely to be of epithelial derivation.

This concise review will cover primary pulmonary tumours which at least contain a neoplastic mesenchymal or sarcomatoid component and are classed as mixed epithelial-mesenchymal ("biphasic") tumours and epithelial tumours which at first sight appear

mesenchymal in origin. Primary benign mesenchymal neoplasms such as lipoma and haemangioma are not covered in this review, except when these are considered in the differential diagnosis. For 'true' malignant mesenchymal tumours, i.e. sarcomas in the lung the first step is to rule out a metastasis because 1) the lung is the most common site of metastatic sarcoma and 2) sarcomas are far more common in the somatic soft tissues than in the lung.

The classification of sarcomatoid pulmonary carcinomas has changed considerably over the years, with criteria often set arbitrarily leading to confusion. In the 2004 WHO classification a separate subheading of sarcomatoid carcinoma comprised a group of carcinomas with mesenchymal sarcomatous appearance. The various entities in this subgroup are now listed as discrete entities in the 2014 WHO classification. As such, sarcomatoid carcinoma is now no more than a descriptive albeit useful term rather than a defined subgroup.

Carcinosarcoma (biphasic- or mixed sarcomatoid carcinoma) is a term to denote malignant epithelial tumours which show clearly identifiable morphological epithelioid and mesenchymal differentiation while acknowledging that both components are essentially of epithelial derivation. Historically "homologous" and "heterologous" variants of

Author for correspondence: Michael A. den Bakker (MD, PhD). Maasstad Hospital, PO Box 9100, 3007 AC Rotterdam, The Netherlands
Email: bakkerma@maasstadziekenhuis.nl
ORCID ID: <https://orcid.org/0000-0001-8996-3134>

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biphasic sarcomatoid carcinoma are recognized, indicating that the carcinomatous component is admixed with a mesenchymal component that has either a simple spindled sarcomatoid morphology (homologous) or a differentiated stromal morphology with for instance osseous, rhabdomyoblastic or chondroid differentiation. The terminology is historical in nature and somewhat imprecise as neither homologous nor heterologous have any bearing with a comparable stromal component in normal lung. The recommended term for homologous sarcomatoid carcinoma is currently pleomorphic carcinoma [1].

Monophasic pulmonary sarcomatoid tumours – Sarcomatoid carcinoma

As mentioned above, sarcomatoid carcinoma is not a single defined entity but is a useful term encompassing the diverse specific entities. The current 2014 WHO classification recognizes 3 specific types of sarcomatoid carcinoma, 1) spindle cell carcinoma (SPCa), 2) giant cell carcinoma (GCCa) and 3) pleomorphic carcinoma (PLCa). The definitions for these tumours are arbitrarily set and have changed conceptually and categorically in the preceding WHO classification schemes, leading to confusion and difficulty when older series are compared to more recent publications. Each of these entities is now morphologically defined but in practice cases with overlapping histological features are frequently encountered. All forms of sarcomatoid carcinoma are high-grade neoplasm with an associated poor prognosis [2].

Spindle cell carcinoma

Spindle cell carcinoma is almost exclusively composed of spindle cells. (Figure 1) The WHO diagnosis is based on morphology, immunohistochemical confirmation of epithelial differentiation is not required. Histologically these highly malignant tumours are composed of fusiform cells with a fascicular architecture, similar to soft tissue spindle cell sarcoma.

Giant cell carcinoma

Pulmonary giant cell carcinoma is a malignant non-small cell carcinoma almost exclusively composed of tumour giant cells with no other differentiated elements. Giant cells

Figure 1-Spindle cell carcinoma: Pneumonectomy for large tumor. Mitotically active proliferation of spindle cells with a fascicular orientation. The cells have nuclei which vary in size and shape, with coarse chromatin; focal necrosis.(H & E X 20)

may be seen in conventional types of lung carcinoma [3], however, the diagnosis is reserved for cases in which the giant cells are the predominant cell. Its identity as a specific tumour type has been questioned in the past, but in many of the older series GCCa was grouped with PLCa and NSCLC types with giant cells as a minor component [3,4]. The giant cells of GCCa may be either mononuclear or multinuclear and are characteristically associated with a neutrophilic infiltrate. The neutrophils may be engulfed or phagocytosed by the tumor cells [5]. (Figure 2)

Figure 2-Giant cell carcinoma: Lobectomy for tumour in a 76-year-old male. Dispersed mononuclear and multinuclear cells with greatly enlarged nuclei which vary in size and shape and contain large nucleoli. In the background a mixed inflammatory infiltrate with a neutrophilic component. This tumour solely stained for vimentin, all other markers including cytokeratins were negative. (H & E x20)

Pleomorphic carcinoma

Pleomorphic carcinoma can either be 1) a carcinoma composed of only spindled cells and giant cells or 2) a carcinoma composed of a morphological differentiated form of non-small cell carcinoma combined with either spindle cells, giant cells or both, with at least 10% of the tumor consisting of spindle and or giant cells. (Figure 3A.) The exception to this rule applies to

Figure 3A - Pleomorphic carcinoma: Pneumonectomy specimen. Pleomorphic carcinoma consisting of a sarcomatous neoplastic spindle cell proliferation with focally squamous cell carcinoma (H & E x 20)

Figure 3B-Pleomorphic carcinoma: Lobectomy (left lower lobe) in a 69-year-old male. Malignant tumour composed of pleomorphic sarcomatoid cells. A couple of cells stained for pan-cytokeratin while the tumour was diffusely and strongly positive for desmin. Other muscle markers, including myf-4, smooth muscle actin and myo-D1 were completely negative. Although the tumour lacks an extensive spindle- or giant cell morphology it is best considered a pleomorphic carcinoma. (H & E x 40)

tumours with a small cell component and tumours with a large cell neuroendocrine (LCNEC) component, which are by definition classed as combined small cell or LCNEC

carcinoma. However, the definition as stated may be too restrictive. For instance cases with sarcomatous cells without typical spindle cell morphology (Figure 3B.) and examples of tumours with a biphasic appearance with a differentiated epithelial component and a sarcomatous undifferentiated component (previously denoted as the homologous type of carcinosarcoma) formally are excluded from the category of pleomorphic carcinoma. Nevertheless, for practical purposes these cases should be diagnosed as pleomorphic carcinoma rather than large cell carcinoma NOS.

Sarcomatoid carcinoma encompassing SPCa, GCCa and PLCa – morphology and immunohistochemistry

There are a limited number of reported series of sarcomatoid cell carcinoma [3,4,6-11]. Older series are summarized in the review article by Pelosi et al. [12] Recently Weissferdt et al. published a large series of sarcomatoid carcinoma which included a subset of spindle cell carcinoma. In a separate publication the clinico-pathological characteristics are documented. The diagnosis of SPCa, GCCa and PLCa is primarily based on morphology, however immunohistochemistry can be a useful adjunct in their diagnosis. In the immunohistochemical analysis of Weissferdt all spindle cell carcinomas stained for cytokeratin CAM5.2 and CK7. Similar findings were reported but with lower staining frequencies in other series [6,8,10,12]. A number of cases expressed TTF1 and/or Napsin and a single case in the series by Weissferdt stained for p40 and CK5. Based on these observations the authors suggest that these cases are reclassified as adenocarcinoma and squamous cell carcinoma respectively [6,7,13].

Although for conceptual reasons this recommendation is understandable, it should be borne in mind that other “non-adeno” carcinomas can express differentiation makers such as large cell neuroendocrine carcinoma (LCNEC) which may express TTF1 in up to 50%. Similarly, p40 may mark non-squamous tumours as well. By definition PLCa with a component of differentiated carcinoma will stain for cytokeratin. Negative or weak staining for CK is reported in a minority of GCCa while TTF1 and p40 are not expressed [14,15]. In a significant number of GCCa, HCG is expressed [3,15]. Given

the rarity of sarcomatoid carcinoma there is sparse data on their genetic background. RAS mutations appear particularly prevalent, while targetable mutations are uncommon [14,16-20]. Interestingly it was recently shown that MET gene mutations are relatively frequent in sarcomatoid carcinoma, in particular exon 14 skipping mutations are found which have been associated with favorable response to crizotinib therapy [21].

Differential diagnosis of sarcomatoid carcinoma

The differential diagnosis understandably comprises other spindle cell neoplasms and sarcomas with giant cells. For SCca in particular monophasic synovial sarcoma, leiomyosarcoma, solitary fibrous tumour (SFT), inflammatory myofibroblastic tumour (IMT) and malignant peripheral nerve sheath tumor (MPNST) should be considered. These sarcomas are exceedingly rare as primary pulmonary neoplasms and can be discounted by additional immunohistochemical stains.

Synovial sarcoma can be ruled out by TLE staining [22] or, albeit less specific the combination of BCL2 and CD99. Molecular analysis can help by identifying the t(X;18) translocation in synovial sarcoma. Leiomyosarcoma will stain for smooth muscle actin, desmin and/or caldesmon staining, but can show focal cytokeratin positivity. MPNST may show focal S100 staining but in the pure spindle cell form will not stain for cytokeratin. In rare cases MPNST may contain epithelial elements, prompting a diagnosis of carcinosarcoma. Loss of staining for H3K27me3 may aid in the diagnosis of MPNST [23]. Solitary fibrous tumour does not stain for cytokeratin and has a characteristic growth pattern, generally with a low-grade cytological aspect and low mitotic activity. Confirmation of the diagnoses is made by staining for CD34 or, more specifically, STAT6 resulting from the NAB2-STAT6 gene fusion [24]. IMT is a spindle cell neoplasm with an extensive inflammatory component, which often obscures the myofibroblastic spindle cell component. The spindle cells appear “activated” but are not overtly hyperchromatic. Smooth muscle actin is positive and up to 50% of IMT’s will stain for ALK1 protein (Figure 4) [25].

Desmoplastic mesothelioma is another consideration in the differential diagnosis with spindle cell carcinoma. Both tumours are cytokeratin positive and spindle cell carcinoma may spread to the pleura and grow diffusely. Mesothelial markers such as calretinin, D2-40 and WT1 are often negative in desmoplastic mesothelioma but conversely stain in sarcomatoid carcinoma [8]. GATA3 staining may aid in the distinction [26] as it is frequently positive in desmoplastic mesothelioma. Loss of BAP1 strongly supports a diagnosis of mesothelioma, however it is fairly insensitive, loss was only observed in 15% of cases in one study [27].

Obviously the main consideration in the differential diagnosis of PLCa and GCCa is a metastasis of a soft tissue sarcoma with giant cells (malignant giant cell tumour of soft parts (MGCT-SP), formerly giant cell malignant fibrous histiocytoma). The recognition of an epithelial differentiated component in PLCa will promptly lead to the correct diagnosis. As mentioned above, the main alternative entities to consider are MPNST with glandular differentiation, which is distinctly uncommon in the somatic soft tissues and vanishingly rare in the lung.

Figure 4-Inflammatory myofibroblastic tumour : Wedge excision of a small tumour in the right upper lobe of a 4-year-old discovered on imaging for suspected pneumonia. Plump spindled cells are diffusely present in an inflammatory background. The spindled cells have enlarged nuclei, however, there is no hyperchromasia. (H & E X20) The ALK1 stain (inset) shows cytoplasmic staining.

Biphasic pulmonary tumours

Neoplasms which have both a morphological epithelial and a mesenchymal stromal

component are considered below. While the appearance suggest that these tumours are derived of separate mesenchymal and epithelial cells it is now accepted that the neoplastic cells are derived from a common precursor which probably undergoes epithelial to mesenchymal transition and thus are essentially epithelial in nature [28]. However, it is the phenotype which determines the tumours biological behaviour.

Benign pulmonary biphasic tumours

Pulmonary (chondroid) hamartoma

Benign pulmonary mixed epithelial-mesenchymal tumours are uncommon. The most commonly encountered mixed tumour, pulmonary (chondroid) hamartoma, is composed of mature cartilage admixed with bronchial epithelial elements, which impart its biphasic appearance. (Figure 5.) However, the epithelial component is now considered entrapped bronchial tissue, thus although pulmonary hamartoma appears biphasic it is essentially a purely mesenchymal tumour. Consistent genetic changes have been documented in pulmonary hamartoma, [29] which would indicate that this a true neoplasm rather than a hamartoma. Further arguments supporting this view are its rarity in childhood and progressive slow growth which, when unchecked, may result in examples of so-called “giant pulmonary hamartoma”. Pulmonary hamartoma is weakly PET positive and may occur in either endobronchial or parenchymal locations. Resection is curative. Multiplicity may occur and should raise concerns about Carneys

Figure 5-Pulmonary chondroid hamartoma: Centrally located tumour in a 69-year-old male. Paucicellular hyaline cartilage associated with peripherally located slit-like bronchiolar structures lined by regular epithelium. (H & E X 20)

triad where pulmonary chondroma (see below) is combined with extra-adrenal paraganglioma and gastric GIST.

Histologically, additional mesenchymal tissue types may be encountered in pulmonary chondroma, including fibroblastic, smooth muscle and adipose tissue, leading to a plethora of alternative names. The differential diagnosis of pulmonary (chondroid) hamartoma will encompass other pulmonary tumours with a chondroid component. Primary pulmonary chondroma is to date considered a different entity, although this view can be challenged, given the now accepted exclusively mesenchymal nature of pulmonary chondroid hamartoma. Pulmonary chondroma is most commonly composed of myxoid chondroid tissue, less frequently they are composed of hyaline cartilage. Compressed respiratory tissue is frequently seen at the interface of tumor and lung but not within the tumour and this feature is more typical of pulmonary chondroid hamartoma. Similarly, the presence of fat, fibrous stroma and smooth muscle is distinctly uncommon in pulmonary chondroma and is indicative of pulmonary chondroid hamartoma. The presence of a hypocellular fibrous pseudocapsule is characteristic and is not seen in pulmonary chondroid hamartoma [30]. Further differential diagnostic considerations include (1) primary pulmonary or metastatic chondrosarcoma, (2) malignant primary lung tumours which may contain chondromatous elements such as carcinosarcoma; (3) teratoma with cartilaginous elements; 4) other benign pulmonary neoplasms which may show chondroid metaplasia (Figure 6). Primary pulmonary chondrosarcoma is exceptionally rare [31,32]. Metastatic chondrosarcoma may be considered when multiple pulmonary tumours are present [33]. Chondrosarcoma, either primary or metastatic will show overt malignant cytological features, setting these apart from pulmonary hamartoma.

Carcinosarcoma with heterologous chondroid tissue is distinguished by the presence of other cell types, including epithelial elements (discussed below). In addition, these tumours show clear malignant features. Cartilaginous tissue in metastatic germ cell tumours in patients treated with chemotherapy may histologically mimic pulmonary chondroma.

Primary pulmonary teratoma is very rare, reported cases have contained cartilaginous tissue as the primary component.

Figure 6-Bronchial lipoma with cartilaginous metaplasia: Endobronchial lipomatous mass in a 78-year-old male. This is a discussion case, the diagnosis of lipoma was preferred over chondroid hamartoma because of the extensive fatty component, the absence of slit-like glandular spaces and the lack of sharp circumscription. (H&E X 20)

Pulmonary adenofibroma

Pulmonary adenofibroma (see Suster & Moran Histopathology 1993) is considered a true mixed epithelial-mesenchymal neoplasm [34]. The stromal component is composed of spindle cells, cytologically and architecturally similar to solitary fibrous tumours, which in most cases express estrogen receptors. The stromal cells are combined with TTF-1 expressing epithelial cells forming a mass with an appearance similar to phyllodes tumour or fibroadenoma of the breast or uterus (adenofibroma)[34]. Recently the stromal cells were shown to harbor a genetic aberration, NAB2-STAT6 fusion, which is identical to that identified in solitary fibrous tumours [35]. While few cases have been reported to date all have followed a benign course.

Pleomorphic adenoma

Although histologically similar to its salivary gland counterpart, pleomorphic adenoma can be considered a biphasic pulmonary tumour. In contrast to other salivary gland tumours pleomorphic adenoma is very uncommon in the lung [36]. Arising from bronchial glandular tissue it is composed of varying proportions of glandular epithelial elements merging with myoepithelial and myxochondroid stromal

elements. Of other primary pulmonary salivary gland tumours a rare variant of epithelial-myoepithelial carcinoma, termed pneumocytic adenomyoepithelioma should be mentioned as this rare variant has an extensive myoepithelial component which appears stromal and imparts a biphasic appearance [37]. However, its immunohistochemical profile is distinct and will facilitate recognition as a salivary gland type of neoplasm (Figure 7) In contrast to typical epithelial-myoepithelial carcinoma, the epithelial component of pneumocytic adenomyoepithelioma expresses TTF1 supporting its pulmonary origin.

Sclerosing pneumocytoma

Sclerosing pneumocytoma (formerly sclerosing haemangioma) shows varying architectural growth patterns and a combination of cell types with epithelial cells lining surfaces of papillae and solid areas and which may form angiomatoid structures. The stromal cells are morphologically and to a certain extent immunohistochemically distinct, but are clonally related to the lining cells [38]. While this rare benign pulmonary neoplasm histologically appears biphasic, the stromal cells do also

Figure 7-Pneumocytic adenomyoepithelioma: Resection of a lung tumour in a 57-year old female. A needle biopsy, which mainly contained the compact stromal component was diagnosed as squamous cell carcinoma because of cytokeratin and p63 staining. The resection specimen is composed of a spindle cell stromal component admixed with glandular elements, neither of which shows high-grade cytology. This is currently considered a variant of epithelial-myoepithelial carcinoma of which very few cases have been reported in the lung. To date all cases have shown benign behaviour.

show epithelial differentiation with staining for EMA and TTF1 (but not cytokeratin). (Figure 8)

Figure 8-Sclerosing pneumocytoma: Tumor resected from the lung of a 53-year old female. Multiple growth patterns are seen including acinar structures partly with sclerotic stroma, papillary formations and solid areas. The tumor is circumscribed but not encapsulated. There is no atypia. The variable architecture and sclerosis may prompt a diagnosis of malignancy but careful attention to the cellular detail should prompt the correct diagnosis. Sclerosing pneumocytoma is distinctly more common in the far east.

Malignant pulmonary biphasic tumours

A number of malignant lung tumours with clear-cut biphasic morphology are recognized. The two prototypical examples are carcinosarcoma and pulmonary blastoma. Intermediate forms exist where the distinction between these tumours becomes blurred.

Pulmonary blastoma

A characteristic rare pulmonary biphasic tumour is pulmonary blastoma (PuBl), defined as a mixed epithelial-mesenchymal tumour of which the epithelial component resembles so-called foetal (-type) adenocarcinoma [39]. Foetal type adenocarcinoma is a distinctive variant of adenocarcinoma in which regular tall epithelial cells which contain glycogen form complex glandular structures. Squamoid morules are generally present. The name derives from the fact that the appearance is similar to that of developing lung in the foetal glandular stage. In this variant of adenocarcinoma sparse myxoid stroma is present of which the cells are not atypical. A high-grade variant is recognized in which the typical foetal epithelial appearance merges with conventional adenocarcinoma but by definition must show at least 50% foetal morphology. The

epidemiology and immune-histology of the high- and low grade variants are different, suggesting that the two types may be unrelated. In particular, the low-grade variant shows nuclear beta-catenin expression, while the high-grade variant shows cytoplasmic and membranous staining. In pulmonary blastoma the epithelial component of foetal adenocarcinoma is combined with a malignant stromal component which commonly is composed of primitive blastemal cells but which may show somatic differentiation along the lines of skeletal muscle, bone or cartilage (Figure 9). Blastoid cells are undifferentiated primitive mesenchymal cells, which typically have coarse dense chromatin and a high nuclear to cytoplasmic ratio. Blastoid cells are a typical component of pulmonary blastoma, where they are combined with a characteristic epithelial component (see below).

Similar to low-grade foetal adenocarcinoma nuclear expression of beta-catenin is a characteristic feature. In contrast to low-grade foetal adenocarcinoma, pulmonary blastoma is more commonly seen in older patients without gender predilection, whereas low-grade foetal adenocarcinoma is seen in a slightly younger age group with female predominance.

Figure 9-Pulmonary blastoma: Resected large tumor from the left lung of a 42-year-old female (A-D). Immature glandular structures formed by cylindrical cells with vacuolated cytoplasm and hyperchromatic coarse chromatin, reminiscent of developing lung (A,B), in combination with malignant stromal tissue. In addition to blastemal cells (C) with dense dark nuclei and a high nuclear-cytoplasmic ratio, differentiated stromal elements composed of malignant appearing cartilage (D) and undifferentiated pleomorphic cells are present.

Pulmonary blastomas are large tumours with a poor prognosis [40]. Genetic analysis of PuBl have corroborated the nuclear beta-catenin staining by identifying CTNNB1 mutation [41,42]. Despite its name and frequent inclusion in reviews of mixed pulmonary tumours, pleuropulmonary blastoma bears no relationship with PuBl. Pleuropulmonary blastoma is a paediatric tumour, which is solely mesenchymal often cystic in nature with rhabdomyoblastic differentiation.

Carcinosarcoma

Similar to its occurrence in other organs, carcinosarcoma is a prototypical biphasic high-grade malignant neoplasm, with a malignant epithelial component and a malignant stromal component. Similar examples are well known in other parenchymal organs, in particular in the uterus (malignant mixed Mullerian tumour). The stromal component of pulmonary carcinosarcoma must show some line of differentiation, such as osseous, chondroid or rhabdomyomatous (Figure 10). Tumours lacking clear evidence of mesenchymal differentiation are better considered as pleomorphic carcinoma (Figure 11). The epithelial component may take the form of any type of non-small cell carcinoma. However, the WHO classification indicates that large cell neuroendocrine carcinoma (LCNEC) with a sarcomatous component should be reported not as carcinosarcoma but as LCNEC with sarcoma. Similarly, the combination of small cell carcinoma (SCLC) with sarcoma should be classified as combined SCLC [1]. Carcinosarcoma is an aggressive tumour seen in smokers in an older age range. There is a distinct male predominance. The epithelial component of carcinosarcoma may also show foetal-type adenocarcinoma as a minor component (Figure 12) [43]. The distinction between carcinosarcoma and pulmonary blastoma with a high grade epithelial component is made by the presence of a considerable proportion of typical “low-grade” foetal-type adenocarcinoma (>50%) and the typical blastemal-type undifferentiated stroma in pulmonary blastoma. Few cases of carcinosarcoma have been molecularly analyzed. EGFR mutations are extremely rare, a single case with an in frame exon 19 deletion has been published [44]. The differential diagnosis of pulmonary carcinosarcoma will

naturally include metastatic deposits from other sites, particularly from the uterus (Figure 13).

Figure 10-Carcinosarcoma: Resected tumour, 69-year-old male. A differentiated epithelial component (top - squamoid) and a stromal component consistent with osteosarcoma (bottom) define this tumor as carcinosarcoma. (H & E X 40)

Figure 11-Pleomorphic carcinoma:

A tumour with morphologically sarcomatous stromal elements but which do not show evidence of somatic differentiation and therefore falls short of criteria for carcinosarcoma and therefore should be considered pleomorphic carcinoma or even large cell carcinoma NOS (H & E X20).

Figure 12-Pulmonary blastoma – carcinosarcoma: A-68-year-old male with a large tumour in left lower lobe. This is a biphasic tumour which on one hand shows features of pulmonary blastoma with typical “foetal-type” adenocarcinoma (A) and a minor component of undifferentiated blastemal stromal cells. However, a high-grade undifferentiated carcinoma component (B) is present and multiple lines of differentiation in the stromal compartment with chondroid (C), rhabdomyoblastic (D) and osteosarcomatous (E) elements are present in addition to pleomorphic sarcoma (F). Immunohistochemical staining confirms the biphasic nature; areas with cytokeratin (AE1/AE3) positivity (G), TTF-1 (H) and skeletal muscle differentiation staining for desmin (I) and Myf4 (J)

Take home points

- Pulmonary tumours with a mesenchymal component are rare, for malignant sarcomatous tumours the first consideration is to rule out a metastasis.
- Sarcomatoid carcinoma is not a singular defined entity in the WHO classification but refers to a group of tumours with sarcomatous features.
- Clear definitions for individual entities are given in the WHO, however, the definitions are set by arbitrary criteria and there is sparse or no scientific evidence for the cut-off values.

Figure 13-Metastatic carcinoma mimicking carcinosarcoma: A tumour which at first sight fulfills all criteria of carcinosarcoma with a differentiated glandular component (A) and malignant chondroid stroma (B). Further investigations revealed that the patient had previously undergone a mastectomy for metaplastic breast carcinoma which morphologically was identical to the lung mass.

- Cases may not comfortably fit in a specific category, however, this does not lead to problems in patient management.
- Specific molecular features are uncommon in this group of tumours with the exception of cMET exon 14 skipping mutations in sarcomatoid carcinoma (as a group) and exon 3 beta-catenin mutations in pulmonary blastoma

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