

Approaches to Tumor Classification in Pulmonary Sarcomatoid Carcinoma

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Abstract: Pulmonary sarcomatoid carcinoma (PSC) is a heterogeneous category of primary lung cancer accounting from 0.3% to 3% of all primary lung malignancies. According to the most recent 2015 World Health Organization (WHO) classification, PSC includes several different variants of malignant epithelial tumors (carcinomas) histologically mimicking sarcomas showing or entirely lacking a conventional component of non-small cell lung cancer (NSCLC). Thus, this rare subheading of lung neoplasms includes pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, pulmonary blastoma, and carcinosarcoma. A diagnosis of PSC may be suspected on small biopsy or cytology, but commonly requires a surgical resection to reach a conclusive definition. The majority of patients with PSC consists of elderly, smoking men with a large, peripheral mass characterized by well-defined margins. However, presentation with a central, polypoid endobronchial lesion is well-documented, particularly in pleomorphic carcinoma and carcinosarcoma showing a squamous cell carcinoma component. As expected, PSC may pose diagnostic problems and immunohistochemistry is largely used when pathologists deal these tumors in routine practice. Indeed, PSC tends to overexpress molecules associated with the epithelial-to-mesenchymal transition, such as vimentin, but the panel of immunostains also includes epithelial markers (cytokeratins, EMA), TTF-1, p40 and negative markers (e.g., melanocytic, mesothelial and sarcoma-related primary antibodies). Although rare, PSC has increased their interest among oncologist community for different reasons: a. identification of the epithelial-to-mesenchymal phenomenon as a major mechanism of secondary resistance to tyrosine kinase inhibitors; b. over-expression of PD-L1 and effective treatment with immunotherapy; c. identification of *c-MET* exon 14 skipping mutation representing an effective target to crizotinib and other specific inhibitors. In this review, the feasibility of the diagnosis of PSC, its differential diagnosis and novel molecular findings characterizing this group of lung tumor are discussed.

Keywords: sarcomatoid, carcinoma, c-MET, PD-L1, cytokeratins, immunohistochemistry, WHO

Basic Concepts of Pulmonary Sarcomatoid Carcinoma

The occurrence of pulmonary carcinomas showing a sarcomatoid or sarcomatous cell component is a well-known phenomenon indicating a divergent tumor cell dedifferentiation from epithelial to mesenchymal phenotype in conventional non-small-cell lung cancer (NSCLC).¹ The term pleomorphic (spindle/giant cell) carcinoma was first introduced in 1994 by Fishback et al² to recognize and better categorize a specific subset of high-grade carcinomas, including unusual variants previously defined inflammatory-type sarcomatoid carcinoma and pseudoangiosarcomatous carcinoma (so-called pseudovascular adenoid squamous cell carcinoma).^{3–10}

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The seminal paper by Fishback et al,² subsequently supported by other similar series,^{11–23} provided the basis of the 2004 World Health Organization (WHO) classification of lung cancers under the designation of “sarcomatoid carcinoma”, then including five main variants, namely pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma.²⁴

According to this statement, overall sarcomatoid carcinoma is a group of poorly differentiated NSCLC (squamous cell carcinoma, large-cell carcinoma and/or adenocarcinoma) containing a component of sarcoma-like elements or true sarcomatous areas. Of note, the occurrence of small-cell carcinoma (SCLC) or large-cell neuroendocrine carcinoma (LCNEC) with sarcoma or sarcoma-like component is considered a combined variant into the category of neuroendocrine neoplasms.^{25,26}

Pleomorphic carcinoma is the most common type of PSC (>50%), followed by spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma.^{2,5,13–16,24}

Several review articles have been performed on this topic and there is general agreement on the pathogenesis of this intriguing tumor entity. Indeed, previous works have consistently evidenced the clonal origin of PSC demonstrating identical mutations of *KRAS* and *p53* in either carcinoma and sarcoma/sarcomatous component,^{27–35} as also disclosed in sarcomatoid carcinoma arising in other sites.^{36–38}

Basically, the appearance of an additional sarcomatoid/sarcomatous component in an otherwise conventional NSCLC is due to up-regulation of the epithelial-to-mesenchymal transition (EMT) secondary to activation of genetic mechanisms generally associated with resistance to chemotherapy and tyrosine kinase inhibitors, such as *KRAS* mutations, *c-MET* gene alterations, overexpression of vimentin, ZEB1, Snail, MiR-34 coupled to down-regulation of E-cadherin and expression of epithelial markers, miR-200, mutations of *EGFR* (Figure 1).³⁹

Epidemiology, Imaging Studies, Clinical Features

Several series of PSC have been published in literature using the current criteria of the WHO classification.^{2,11–23} Overall, the incidence of PSC ranges from 0.3% to 3% of all lung malignancies with a significant higher prevalence in male gender, current/former smokers. The median age at diagnosis is about 65 years, although pulmonary blastoma usually affects younger smokers without gender predilection.

Pelosi et al⁷ in a series of 92 PSC reported a male/female ratio of about 4:1, with 90% of smoking patients. As in conventional NSCLC, PSC may occur also in patients under the age of 40 years and non-smokers,⁴⁰ while even asbestos exposure seems to have a promoting role in PSC.⁴¹

At imaging studies, PSC may present as either a central or peripheral location.^{2,5,24,42} Pleomorphic carcinomas with squamous cell carcinoma component and carcinosarcoma may show a peculiar endobronchial, polypoid appearance (Figure 2), while peripheral PSC typically manifests as a large mass (over 10 cm) with rounded, well-defined margins (Figures 3 and 4) with necrotic and/or hemorrhagic areas and soft surface with/without cavitation (Figure 5).

Clinical symptoms are generally non-specific and basically related to the tumor location and involved structures, such as main bronchi, mediastinal infiltration, and chest wall.^{5,7}

Of note, giant cell carcinoma is often characterized by peripheral neutrophilia and fever due to production of granulocyte colony-stimulating factor (G-CSF) or other paraneoplastic symptoms.^{43,44}

A summary of the most characteristic features of patients with PSC is reported in Table 1. As conventional NSCLC, PSC may metastasize through lymphatic channels and blood vessels leading to usual distant metastases (i.e., brain, bone, adrenal gland, liver), but unusual sites (i.e., pancreas, and kidney) and involvement of the digestive tract are not infrequent.^{5,7,45,46}

The overall survival of stage-matched, surgically resected PSC is generally worse than that observed in conventional NSCLC. This finding has been further confirmed by some large series of PSC.^{15,16}

The median survival is about 10 months and the estimated 5-year survival rate 15%.^{15,16} In the recent study of the Mayo Clinic, multivariate analysis showed that T and M stage, and surgery plus neoadjuvant or adjuvant therapy were significant prognostic parameters.^{15,16} At matched analysis, PSC confirmed a worse survival when compared with adenocarcinoma and squamous cell carcinoma.

PSCs are staged as for other NSCLC, according to the most recent edition of the AJCC/UICC/IASLC staging system.

Diagnosis of Pulmonary Sarcomatoid Carcinoma According to the WHO Classification

The classification of sarcomatoid carcinomas of the lung has posed significant challenges over the years, mainly based on their rare occurrence, heterogeneous histology, and unclear

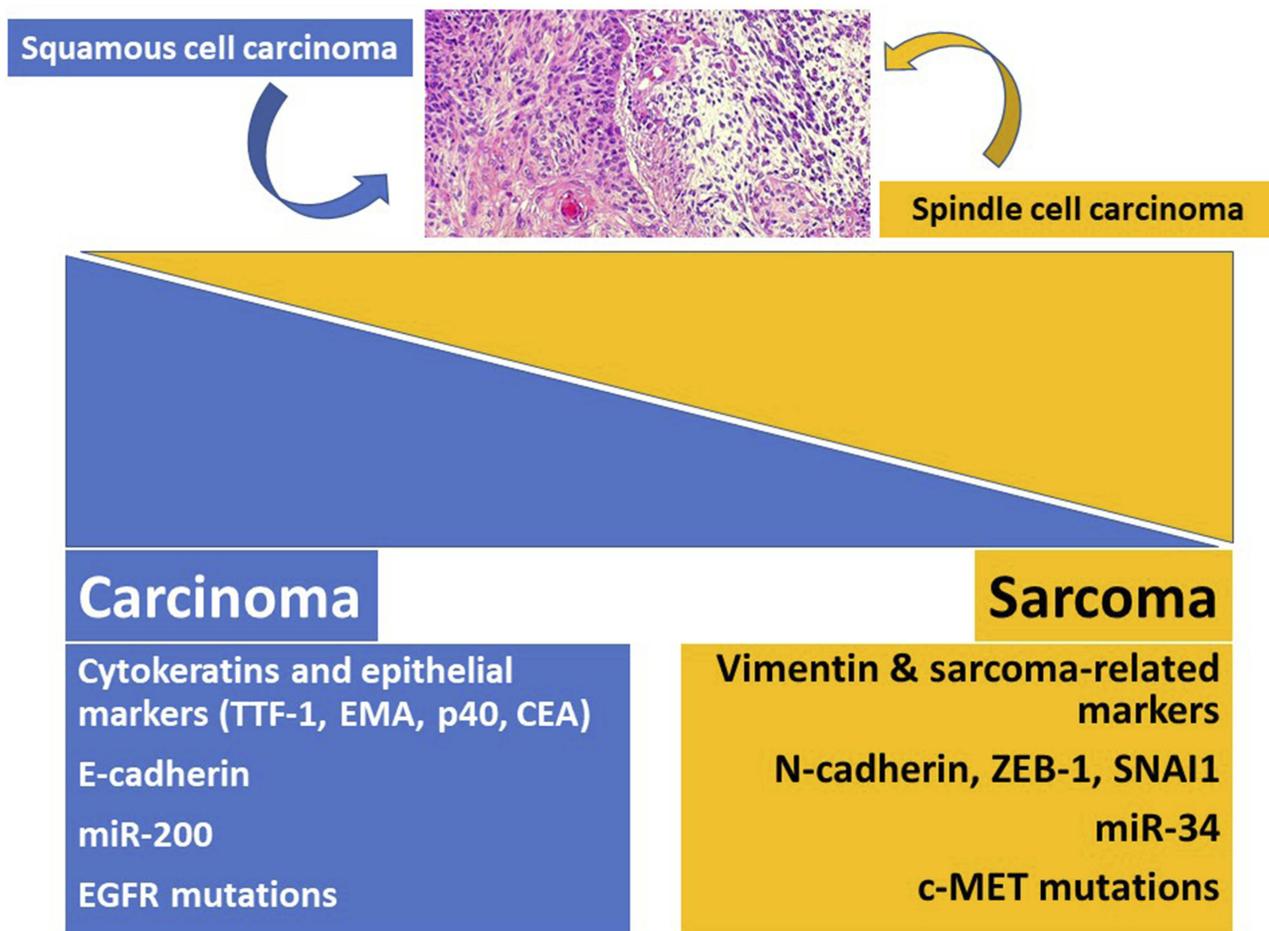


Figure 1 A concise scheme illustrating the balance of epithelial-to-mesenchymal transition markers in sarcomatoid carcinoma sustained by up- and down-regulation of different molecules and gene alterations governing the tumor cell cellular program.

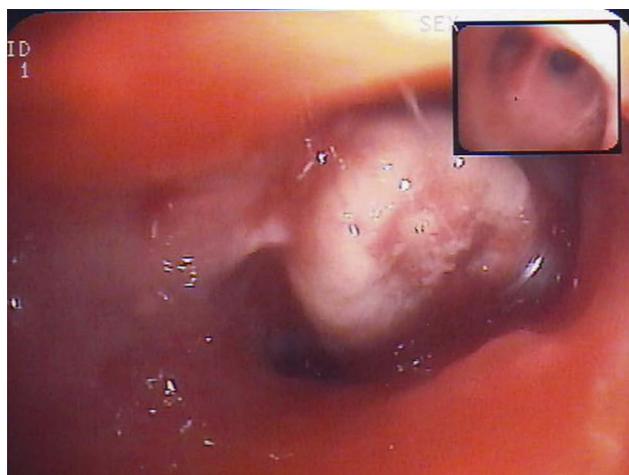


Figure 2 Bronchoscopy showing a whitish polypoid lesion consistent with carcinosarcoma at histology.

histogenesis. This led to multiple changes along their subsequent WHO classifications, both in terms of diagnostic criteria and nomenclature. Moreover, alternative descriptive

classifications have been formulated, which encompass the following: monophasic and biphasic lesions, the latter further subdivided into homologous or heterologous neoplasms.^{4,47}

The 2004 WHO classification established the unification of a spectrum of histological subtypes under the generic term of sarcomatoid carcinoma, which includes pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and blastoma.⁴⁸ Since then, no significant changes have been made as the current 2015 WHO classification basically adopts the same terminology and diagnostic criteria with few recommendations, mainly regarding molecular tests for predictive gene alterations.^{24,49} Importantly, most of the entities encompassed under the definition of PSC can be recognized from their morphological features, with immunohistochemical stains being necessary only in a subset of cases (Table 2).

More in details, in the current WHO classification, pleomorphic carcinoma is defined as a poorly differentiated

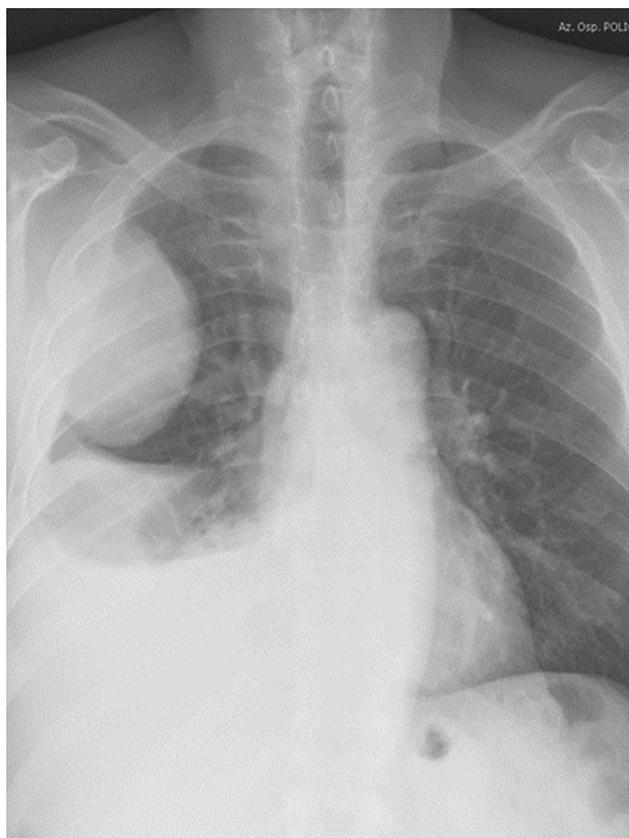


Figure 3 Sarcomatoid carcinoma of the right lung presenting as a large, rounded mass at chest X-rays.

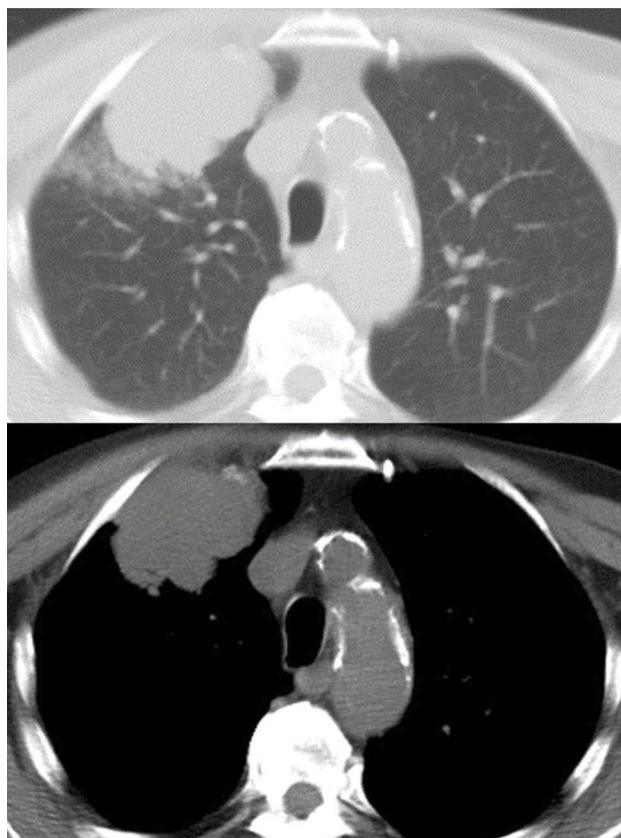


Figure 4 Sarcomatoid carcinoma appearing as a large nodular lesion of the right upper lobe with relatively well-defined margins at computed tomography of the thorax.



Figure 5 Macroscopic appearance of a pulmonary carcinosarcoma consisting of a large (>10 cm), whitish and fleshy mass with well-demarcated tumor border and heterogeneous cut surface.

NSCLC (squamous cell carcinoma, adenocarcinoma, or large cell carcinoma) containing at least 10% of spindle cell and/or giant cell component, or a carcinoma consisting exclusively of spindle and giant cells (Figure 6). The occurrence of different histotypes of carcinoma varies widely across

studies, with adenocarcinoma representing the most frequent finding, up to 73% of the cases.^{2,50,51} Spindle cells and/or neoplastic giant cells can be found intimately admixed with differentiated carcinomatous elements. Once identified, the NSCLC component should be mentioned in the report. Malignant spindle cells generally consist of fusiform elements with eosinophilic cytoplasm, arranged in sheets and fascicles. However, a certain degree of morphological variability exists: slender cells with fibroblastic appearance can be seen admixed with frankly epithelioid elements, displaying large nuclei and prominent nucleoli (Figure 7). Vascular invasion is very common in spindle cell carcinoma even in the bland-looking inflammatory type. A meticulous examination of the vessel wall, also using a pan-cytokeratin stain, is crucial to diagnose spindle cell carcinoma (Figure 8). Giant tumour cells are often discohesive, with multiple nuclei or a single pleomorphic nucleus, which can assume anaplastic and bizarre features; their cytoplasm is typically abundant and eosinophilic, sometimes characterized by neutrophil emperipolesis (Figure 9). These cells are embedded in a variably fibrous to myxoid stroma.

Table I Characteristics Possibly Indicating a Patient with Pulmonary Sarcomatoid Carcinoma

		Additional Notes
Clinical features	<ul style="list-style-type: none"> • Male >> Female • Smoker >> Former >> Never smoker • 60–70-years-old 	<ul style="list-style-type: none"> • Negative neoplastic history
Imaging studies	<ul style="list-style-type: none"> • Large peripheral mass with smooth, well-defined margins and heterogeneous appearance • Polypoid endobronchial lesion 	
Symptoms	<ul style="list-style-type: none"> • Nonspecific • Serum markers nonspecific 	<ul style="list-style-type: none"> • Fever with serum neutrophilia due to G-CSF production or gynecomastia due to beta-HCG production in giant cell carcinoma
Cytology/ Biopsy	<ul style="list-style-type: none"> • Diagnosis of possibility when atypical spindle and/or giant cells or heterologous sarcomatous elements accompany conventional NSCLC component 	
Ancillary techniques	<ul style="list-style-type: none"> • Expression on cytology, cell block or biopsy of CKs, TTF-1, p40 or p63, EMA 	<ul style="list-style-type: none"> • Negative markers excluding sarcomas may be helpful

Abbreviations: NSCLC, non-small-cell lung carcinoma; CK, cytokeratin; EMA, epithelial membrane antigen; TTF-1, thyroid transcription factor-1; HCG, human chorionic gonadotrophin; PSC, pulmonary sarcomatoid carcinoma; G-CSF, granulocyte-colony stimulating factor.

Spindle cell carcinoma and giant cell carcinoma are almost entirely composed of spindle-shaped and malignant giant cells, respectively, without differentiated carcinomatous elements. Histological characteristics are superimposable to those previously described. Caution should be used to distinguish between spindle cell carcinoma and desmoplastic stroma. In this regard, cytological atypia and mitotic activity favour the diagnosis of carcinoma. However, immunohistochemistry may be of help in difficult cases. In addition, an inflammatory background is frequently found in association with these variants.

Carcinosarcoma is a mixture of NSCLC and true sarcomatous elements (rhabdomyosarcoma, chondrosarcoma, osteosarcoma, liposarcoma, leiomyosarcoma, angiosarcoma or combinations of these elements) (Figure 8). Again, pathological report should list all histological types. In a classical study, the most frequent epithelial component was squamous cell carcinoma, followed by adenocarcinoma, adenosquamous carcinoma, and large-cell carcinoma.¹⁷ Nonetheless, a component of high-grade in well-differentiated fetal adenocarcinoma/clear cell carcinoma represents a non-negligible finding; in such cases, the term carcinosarcoma should be used instead of the traditional expression “blastomatoid variant of carcinosarcoma”, according to the WHO scheme.^{24,49} Combinations of neuroendocrine components and sarcoma-containing heterologous elements are exceedingly rare, and the WHO recommends to classify these cases

as “small-cell lung carcinoma or large-cell neuroendocrine carcinoma with associated sarcomatous elements”. Along with the most common sarcomatous elements, cases displaying liposarcoma or angiosarcoma components have been described, although rarely.^{52,53} Less differentiated sarcomatous components with spindle or round cell features can also be observed in the background of more differentiated sarcomatous elements.

Finally, pulmonary blastoma is defined as a biphasic tumour that contains both fetal adenocarcinoma (low-grade/well differentiated) and a primitive mesenchymal stroma, which occasionally has foci of differentiated sarcoma (Figure 10). The epithelial component is characterized by irregularly branching glandular structures, lined by pseudostratified columnar cells with clear cytoplasm and little nuclear atypia, thus resembling the fetal lung in the pseudoglandular phase. Despite the generally bland appearance, foci of cellular atypia consistent with fetal or conventional adenocarcinoma can be found in up to a third of cases.⁵⁴ In most cases, solid cell aggregates (morules) can be noted. The occurrence of a neuroendocrine epithelial component such as small-cell carcinoma is overtly rare in pulmonary blastoma, whereas sparse neuroendocrine cells represent a common finding. An embryonic stroma composed of oval cells with high nuclear-to-cytoplasmic ratio is present by definition, but in a subset of cases (up to 25%) heterologous elements such as osteosarcoma, chondrosarcoma and rhabdomyosarcoma can be identified.

Table 2 Diagnostic Criteria of Pulmonary Sarcomatoid Carcinomas

	Basic Histologic Features	Immunohistochemistry	Additional Notes	Differential Diagnosis
Pleomorphic carcinoma	An NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous carcinoma) with at least 10% of spindle and/or giant cell component	CKs, EMA, TTF-1 and napsin (in case of adenocarcinoma differentiation), p40 and high-molecular-weight CKs (in case of squamous cell carcinoma)		Metastasis from similar biphasic tumors elsewhere (particularly mesothelioma and mixed Mullerian tumors of the gynecological tract)
Spindle cell carcinoma	Pure monophasic spindle cell proliferation with/without inflammatory infiltrate, lacking any NSCLC component	CKs, EMA, TTF-1 and napsin (in case of adenocarcinoma differentiation), p40 and high-molecular-weight CKs (in case of squamous cell carcinoma)	Peculiar vascular invasion/ angiotropism	Primary/secondary sarcomas (inflammatory myofibroblastic tumor, leiomyosarcoma, synovial sarcoma, others)
Giant cell carcinoma	Pure, monophasic discohesive giant cell proliferation, lacking any NSCLC component	CKs, EMA, TTF-1 and napsin (in case of adenocarcinoma differentiation), p40 and high-molecular-weight CKs (in case of squamous cell carcinoma)	Emperipolesis phenomenon	Melanoma, anaplastic/large cell lymphoma, histiocytic sarcoma, pleomorphic undifferentiated sarcoma
Carcinosarcoma	NSCLC with heterologous sarcomatous component (leiomyosarcoma, osteosarcoma, rhabdomyosarcoma, chondrosarcoma, liposarcoma, angiosarcoma)	CKs, EMA, TTF-1 and napsin (in case of adenocarcinoma differentiation), p40 and high-molecular-weight CKs (in case of squamous cell carcinoma) Markers of sarcomatous differentiation		Metastasis from carcinosarcoma elsewhere (particularly gynecological tract); primary (biphasic synovial sarcoma) and metastatic sarcomas
Blastoma	Fetal type adenocarcinoma with primitive mesenchymal blastematous stroma, occasionally demonstrating rhabdomyosarcomatous differentiation	CKs, CK7, TTF-1 and napsin expression in the adenocarcinoma; vimentin in blastematous stroma (myogenic markers in case of rhabdomyosarcoma component)		Primary or metastatic biphasic sarcomas

Abbreviations: NSCLC, non-small-cell lung carcinoma; CK, cytokeratin; EMA, epithelial membrane antigen; WT-1, Wilm's tumor-1; TTF-1, thyroid transcription factor-1; PSC, pulmonary sarcomatoid carcinoma.

Immunohistochemistry

The diagnosis of PSC is mainly based on morphological features, although immunohistochemical stains can be helpful to highlight the different cell components that characterize these tumours (Table 3). This is particularly useful to demonstrate carcinomatous differentiation in small biopsies or in those cases lacking an unambiguous epithelial component despite thorough sampling, thus prompting differential diagnosis with true sarcoma. As expected, the differentiated epithelial component stains with cytokeratins and other markers including epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA), whereas the sarcomatoid component often displays immunoreactivity with vimentin and fascin.⁷ In most cases, a single pancytokeratin

antibody is sufficient to confirm the carcinomatous differentiation of spindle cell/giant cell components, while the use of AE1/AE3 alone or in combination with Oscar is highly recommended compared with other pools that proved less sensitive.⁵⁵ Of note, different cytokeratin filaments can be detected in PSC according to the subtypes of epithelial cells: high-molecular-weight cytokeratins (i.e. 34 β E12 and 5/6) are found in squamous and adenosquamous carcinoma and low-weight cytokeratins (i.e. 7, 8 and 18) in adenocarcinoma and large-cell carcinoma.^{7,56} In particular, CK7 represents a sensible marker to highlight the spindle/giant cell component and was identified in up to 78% of cases in a recent study,⁵⁷ in keeping with previously reported rates of 60-70%.¹⁴

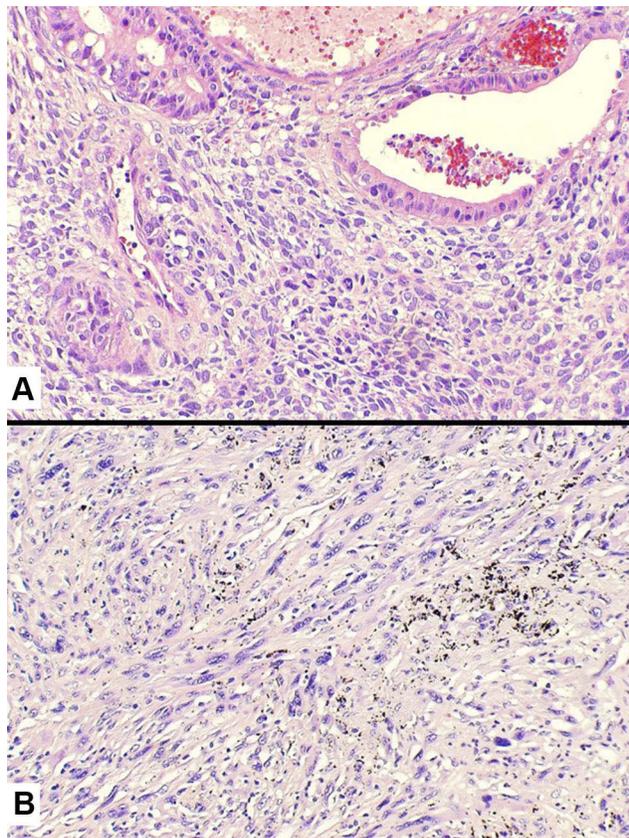


Figure 6 Histology of pleomorphic carcinoma revealing an adenocarcinoma (at the top) intermingled with neoplastic spindle cell component (A). Pure spindle cell carcinoma (B) consisting of a dense and irregular proliferation of atypical spindle cells with marked nuclear atypia and eosinophilic cytoplasm.

Although cytokeratins have significant diagnostic value in sarcomatoid carcinomas, staining is often focal and weak, and some cases can even be completely negative with a number of antibodies. In these cases, additional markers can be helpful, with thyroid transcription factor-1 (TTF-1) demonstrating higher sensitivity than Napsin A for the detection of sarcomatoid carcinoma.^{55,57} Markers associated with squamous differentiation, including p63, p40, and Desmocollin-3, have been repeatedly tested in sarcomatoid carcinomas of the lung. Among these, p63 showed the highest sensitivity (50%) and diagnostic utility, being positive in the spindle cell component of 2/4 cases, where staining for pan-cytokeratins and EMA was completely negative.⁵⁸ On the other hand, p40 and Desmocollin-3 were expressed in the spindle/giant cell elements in 8% and 3% of cases, respectively.⁵⁷ Nevertheless, a word of caution on p63 expression is necessary, since this marker is characterized by low specificity (i.e., positivity in high-grade lymphomas).⁵⁹ A modified histological score for Vimentin (M-VHS), an intermediate filament involved in the EMT, has also proved a valuable tool for diagnosing sarcoma-

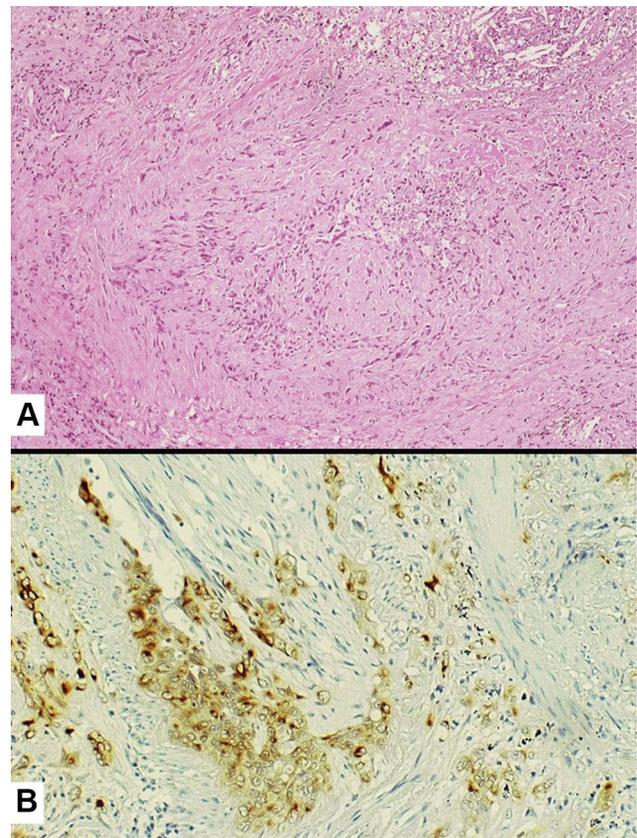


Figure 7 Tumor cell infiltration of a medium-sized vessel wall by spindle cell carcinoma (A) also highlighted by the expression of pan-cytokeratins (clone CAM5.2) (B).

like lesions with spindle and/or giant cells changes, especially in small biopsies. Indeed, an intense and diffuse expression of vimentin strongly supports the diagnosis of pulmonary sarcoma.⁶⁰ Finally, the observation of patchy reactivity with mesothelioma-associated markers (Calretinin and D2-40) in a subset of PSC suggests to include sarcomatoid mesothelioma in the differential diagnosis.⁶¹

In carcinosarcoma, immunohistochemistry is required to demonstrate a poorly differentiated sarcomatous component which cannot be recognized from morphology. Most of these cases harbour a rhabdomyosarcomatous component which can be highlighted with skeletal muscle markers such as myogenin and desmin. In the same way, S100 will confirm a chondrosarcomatous component. On the other hand, cytokeratins allow to demonstrate the epithelial component, with TTF-1 and p63 being particularly useful in cases of adenocarcinoma and squamous cell carcinoma, respectively.^{14,17}

In pulmonary blastoma, the epithelial component stains with cytokeratins, EMA, CEA, TTF-1. In particular, TTF-1 and GATA-6, a fetal lung transcription factor, proved useful

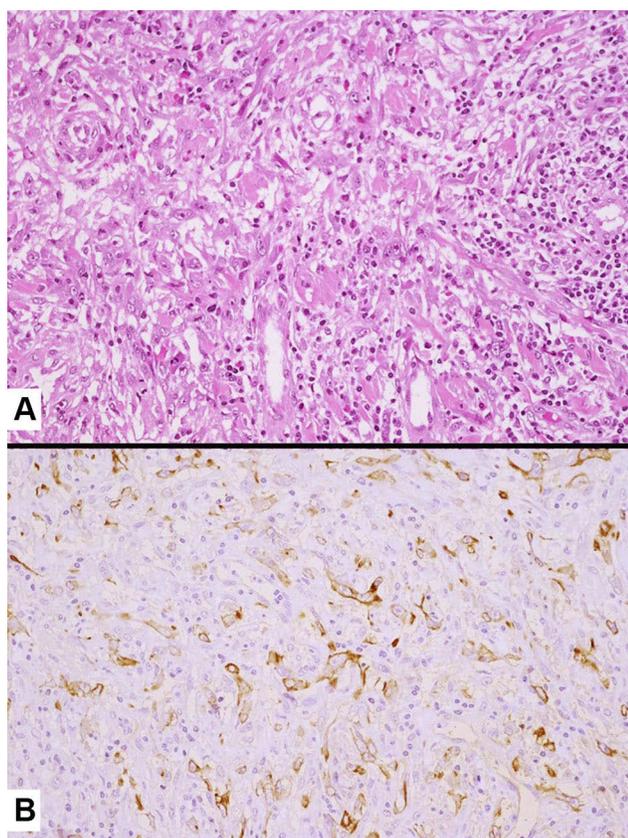


Figure 8 Inflammatory-type spindle cell carcinoma showing a chaotic proliferation of spindle cells with prominent nucleoli into collagenized stroma with a mixed inflammatory infiltrate (A). Positive staining with pan-cytokeratins (clone AE1/AE3) revealing the epithelial/carcinoma differentiation of spindle elements (B).

to highlight the morules.⁶² The mesenchymal component can express smooth muscle actin and vimentin, whereas desmin and myogenin are found in cases showing rhabdomyosarcoma elements; pancytokeratins (AE1/AE3) can also show focal positivity.⁶³ The occurrence of neuroendocrine differentiation, with consistently positive chromogranin, neurone-specific enolase (NSE) and polypeptide hormones, is seen mainly within morules in up to two-third of cases.⁵⁴ Finally, nuclear and cytoplasmic staining of β -catenin in both tubular structures and blastematos component of pulmonary blastoma prompts differential diagnosis with the blastomatoid variant of carcinosarcoma.⁶⁴

Diagnosis of Sarcomatoid Carcinoma in Selected Conditions: Cytology/Small Biopsy and Intraoperative Examination

Some entities in lung cancer require a large amount of tumor tissue to achieve a correct and reliable diagnosis, including

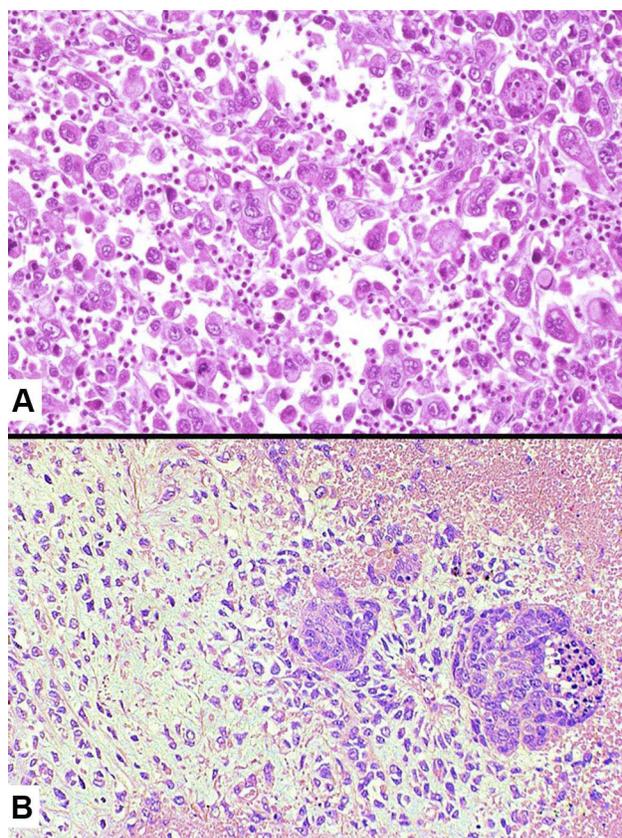


Figure 9 Histology of giant cell carcinoma showing a disorganized proliferation of bizarre, large tumor cells and the presence of sparse inflammatory infiltrates focally involving the cytoplasm of tumor cells (emperipolesis) (A). Carcinosarcoma consisting of a poorly differentiated squamous cell carcinoma (right) with a heterologous chondrosarcomatous component (left) (B).

PSC. By definition, definitive diagnosis is not possible on small biopsy or cytology in light of the requirement for a sarcomatoid/sarcomatous component in at least 10% of the neoplasm.^{24,49} Nevertheless, a diagnosis of “NSCLC with sarcomatoid/sarcomatous component, possible sarcomatoid carcinoma” is reasonable.⁷

Indeed, in an adequate sample, smeared cytology, cell-block or small biopsy may contain either malignant epithelial components (adenocarcinoma or squamous cell carcinoma) and sarcomatoid elements, namely spindled and/or giant neoplastic cells. Akin to neoplastic cells, the background may also contain a significant rate of inflammatory cells (mainly neutrophils and lymphocytes).^{64–66} The spindle and giant cells usually show loss of intercellular cohesion, mitotic figures and necrotic debris. In small biopsy/cell block, the finding of epithelial component through serial haematoxylin–eosin sections and/or immunostains with pan-cytokeratins (low to high-molecular-weight, such as AE1/AE3, MNF116, CAM5.2), EMA, p40, TTF-1, CEA is extremely helpful (Figure 11).

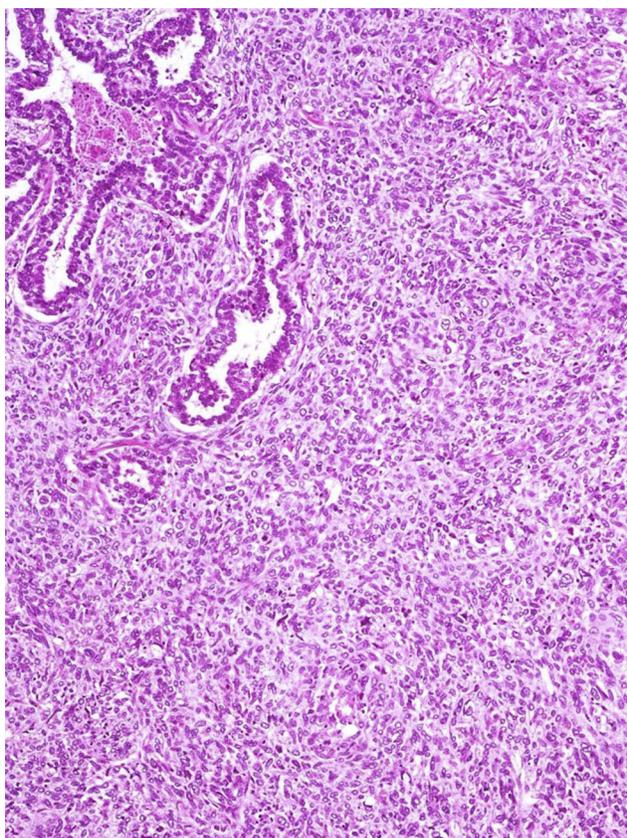


Figure 10 Pulmonary blastoma showing a minor component of well-differentiated adenocarcinoma (top) admixed with an undifferentiated blastematos component.

A prompt diagnosis of PSC during frozen section examination may be a real challenge, even in the hands of expert pathologists. Knowledge of the clinical history of previous neoplasms and careful search for an NSCLC

component using serial sections and/or analysis of more samples are mandatory. In any case, a provisional diagnosis of NSCLC is entirely adequate for practical purposes to guide the surgical procedure.⁷

At intraoperative examination or definitive gross sampling, abundant tumor sampling is crucial in the diagnosis of PSC, particularly when facing with a huge mass (at least 1 block per centimeter of the entire tumor size is necessary).

The differential diagnosis may include several tumors with various cell differentiations and non-neoplastic conditions. Primary or metastatic monophasic and biphasic sarcomas (i.e., synovial sarcoma, malignant solitary fibrous tumor, inflammatory myofibroblastic tumor), sarcomatoid mesothelioma, spindle cell melanoma, sarcomatoid thymic carcinoma, choriocarcinoma are the main neoplastic lesions entering in differential with PSC (Table 2).^{5,7,65–75}

Even benign spindle cell lesions (i.e., desmoid tumor, inflammatory pseudotumor, organizing pneumonia) may mimic malignant spindle cell carcinoma.⁷⁶ This is particularly true at frozen section or in small biopsy when extensive immunostains and molecular analysis (i.e., *SYT-SSX* fusion gene indicating synovial sarcoma) are not accessible or have several limitations, respectively. Nevertheless, pathologists should keep all these diagnostic options in differential diagnosis with PSC.

Among sarcomatoid/sarcomatous lesions in the thoracic region, PSC and sarcomatoid mesothelioma may overlap clinical presentation (i.e., localized malignant mesothelioma) and morphology. Pathologists should keep in mind that immunostains indicating mesothelial and epithelial

Table 3 Ancillary Techniques in Differential Diagnosis Between Pulmonary Sarcomatoid Carcinoma and Mimicking Tumors

	Confirmatory Immunostains	Additional Notes	Molecular Findings
PSC	CKs, EMA, TTF-I, napsin, p40 (depending on the original cell differentiation)	Expression of sarcoma-related markers in heterologous component of carcinosarcoma	
Sarcomas	Myogenic markers (smooth-muscle actin, desmin, h-caldesmon, myogenin), S100, vascular markers (ERG, CD34, CD31), beta-catenin (desmoid tumor), STAT6 (solitary fibrous tumor)	Some types of sarcoma may express CKs (e.g., angiosarcoma, synovial sarcoma, malignant SFT)	SSX/SYT fusion (synovial sarcoma); EWSR1/CREB1 (myxoid sarcoma);
Melanoma	S100, HMB45, Melan-A, SOX11, tyrosinase, MiTF		
Mesothelioma	Calretinin, CK5/6, D2-40, WT-1, BAP-1 (negative staining favors mesothelioma)	Expression of CK7 and CK5/6 may be shared with PSC	
Other: choriocarcinoma	CKs, beta-HCG	Some giant cell carcinoma may express beta-HCG	

Abbreviations: NSCLC, non-small-cell lung carcinoma; CK, cytokeratin; EMA, epithelial membrane antigen; WT-1, Wilm's tumor-1; TTF-1, thyroid transcription factor-1; HCG, human chorionic gonadotrophin; PSC, pulmonary sarcomatoid carcinoma; SFT, solitary fibrous tumor.

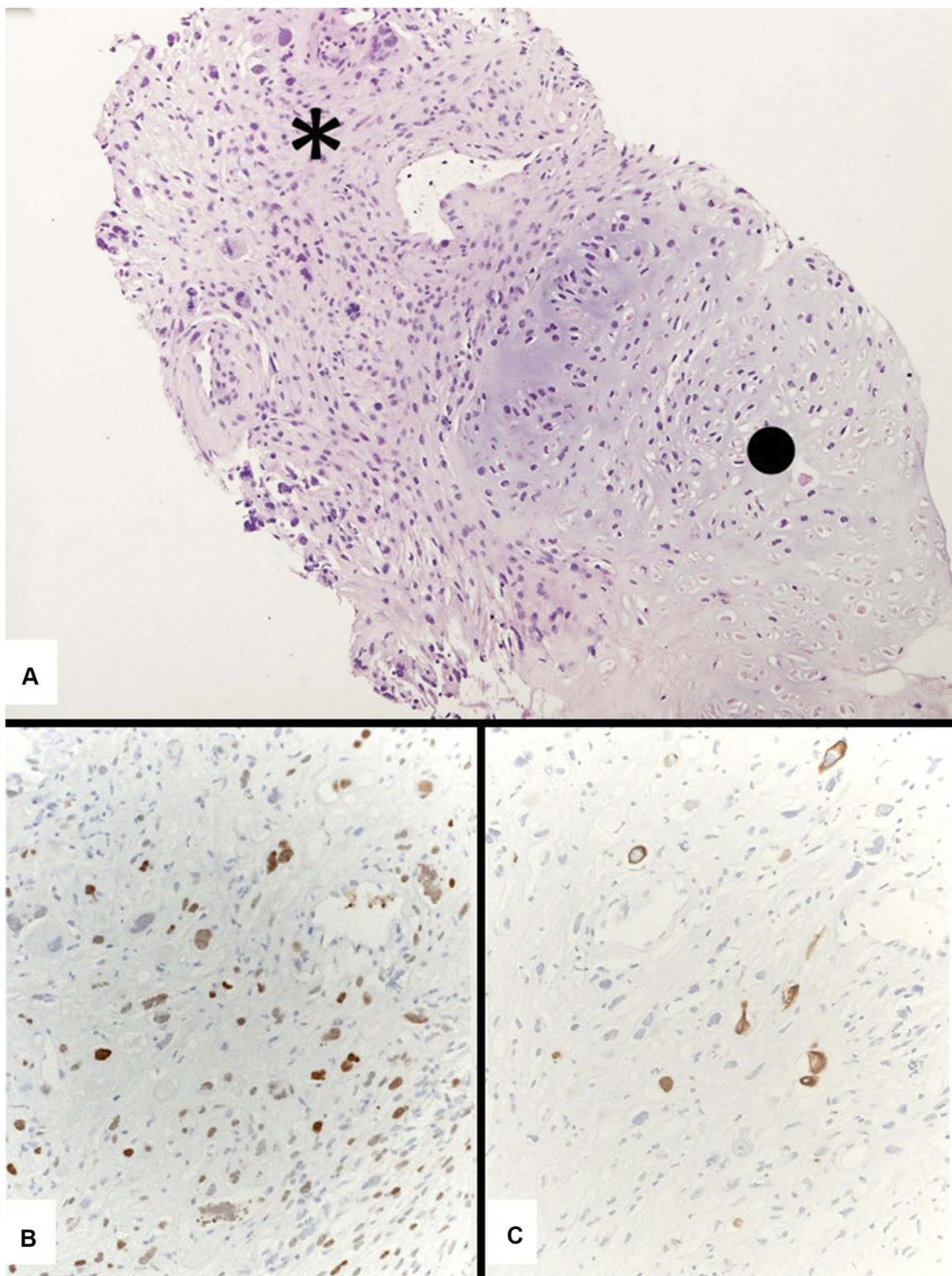


Figure 11 A generous transthoracic biopsy consistent with a carcinosarcoma showing an undifferentiated spindle cell carcinoma (asterisk) and a heterologous chondrosarcoma (dot) (A). Immunostains with pan-cytokeratins (clone MNFI 16) (B) and TTF-1 (clone 8G7G3/1) (C) demonstrate the epithelial adenocarcinomatous differentiation of the spindle cell component.

phenotype may be aberrantly expressed either in PSC and mesothelioma.⁷⁷ A careful evaluation of clinicopathologic and imaging information with histology, immunohistochemistry and molecular biology has been advised to render the correct final diagnosis. Of note, BAP-1 negativity at immunohistochemistry may be very helpful in ruling out PSC and favouring mesothelioma.⁷⁸

Recent Insights into PSC Genetic and Transcriptional Features

PSCs are a highly peculiar and biologically fascinating forms of NSCLC,^{2,5,14} characterized by highly aggressive clinical behaviour with dismal outcome and variable response to chemo-radiotherapy.^{79,80} Owing to their rarity, the genetic events and molecular pathways that account for PSC development and progression have been eluded for a long time and recently, began to emerge.

The first clues about the genetic landscape of PSC became available only in the most recent years.^{81–86} The raise and rapid expansion of the new sequencing techniques, together with the collection of relatively large series of PSC samples available for the analysis have represented major turning points in getting clues into the genetic assets of these tumors.

In 2015 Fallet and colleagues described the first multi-targeted genetic analysis on a large cohort of PSCs.⁸¹ Using the LungCarta Panel on the Sequenom platform these Authors investigated the mutational assets of 26 oncogenes in 114 surgically resected PSCs. They reported mutations in *TP53* (22.6%) *KRAS* (27.2%), *EGFR* (22.2%) and *STK1* (7.4%) as the most common genetic alterations in these lesions. Additional but less frequent alterations were found in *NOTCH1*, *NRAS*, and *PI3KCA*. In 2016, Schrock et al used a deep sequencing approach to map whole-exome mutations in a cohort of 125 PSCs.⁸² While confirming that mutations in *KRAS* (34.4%) and *TP53* (73.6%) are the most common mutations in PSCs, the results of these study refined the frequency of mutations and called into questions other relevant oncogenes that were not present in the Sequenom panel. In particular, these authors showed that PSCs are characterized by a quite high tumor mutational burden (TMB, average of 8.1 mutations/Mb) and that both *TP53* mutated tumors and *KRAS* mutated tumors were characterized by a higher TMB than WT samples.

TP53 mutations were found in a consistent part of PSCs analyzed in this study and were reported to be

widely heterogeneous as subsequently confirmed by other reports.⁸³ Furthermore, the occurrence of *TP53* mutations in PSCs seemed to underpin a specific genetic subtype. For instance, mutation in *NF1* and *RBI* were reported to preferentially occur in *TP53* mutated vs wild-type samples while *NF2* mutations were more frequent in *TP53* wild-type samples, thus hypothesizing distinct evolution pathways for PSCs with different genetic assets. Besides *TP53* and *KRAS* mutations, additional frequent alterations were found, including those in *CDKN2B* (23.2%), *CDKN2A* (37.6%), *MET* (13.6%) and *NF1* (17.6%). Noticeably, mutations in *EGFR* (8.8%) were detected at a lower frequency than previously reported and *BRAF* alterations (7.3%) were limited to a reduced number of PSC samples. Even if providing new important clues into the genetic event of PSCs, these data did not highlight genetic specificity that separates PSCs from NSCLCs. In this regard, the work by Liu et al⁸³ has marked a major point. By means of whole-exome sequencing, the Authors identified mutations in the exon 14 of *MET* as preferentially associated with PSC.

MET exon 14 skipping mutations already described in other tumors including NSCLC affect either donor or acceptor splice site between exon 13 and exon 14, causing a 47 amino acid deletion in the juxta-membrane domain of the MET proteins. This region is crucial for the correct homeostasis of MET signaling being the docking site for the c-CBL ubiquitin E3 ligase (Y1003).^{87,88} Loss of c-CBL binding either by point mutations in the accepting site or by exon 14 skipping, leads to MET stabilization and constitutive activation of MET-dependent signaling.⁸⁸ As in NSCLC, in PSC *MET* exon 14 mutations were mutually exclusive with other oncogene mutations like *KRAS*, *BRAF*, *EGFR* or *ALK* rearrangement, but co-occurrence with *PI3K* mutations has been reported.^{82,83} Furthermore, at least in the original report, *MET* exon 14 mutations were exclusively found in pure PSCs or PSCs with an ADK component.^{83,89} Noticeably, while *MET* exon 14 mutations occur in about 3% of NSCLCs (according to TCGA data), up to 32% of PSCs are reported to carry this alteration. Indeed, according to a recent systematic meta-analysis,⁹⁰ the incidence of *MET* exon 14 mutations in PSC is variable. Overall, its frequency in NSCLC is 2% in adenocarcinoma, 1% in squamous cell carcinoma, 6% in adenosquamous carcinoma and 13% in PSC. Despite the different characteristics of analyzed case series, *MET* exon 14 mutations seem to occur particularly in PSC, ranging from 3% to 31.8%.^{81–83,87–93} The particular attention focused on *MET* exon 14 skipping mutations is then related to the

relatively high frequency of this genetic alteration in PSC histology when compared with other conventional NSCLC, also predicting a good clinical response to MET inhibitors. The rate of *MET* exon 14 mutations is significantly higher in case series including PSC without common targetable mutations in *EGFR*, *KRAS*, *ALK*, *ROS1*, and *RET*.^{92,93} Nevertheless, whenever possible all histological types of NSCLC should be investigated for this mutation.

Activation of *MET* signaling is frequently associated and functionally supports the Epithelial to Mesenchymal Transition (EMT),^{90,91} which is believed to be a driver mechanism in the progression of PSC from well-differentiated lesions.

The frequent coexistence of both well-differentiated and sarcomatoid components within the same lesions led to the common assumption that PSCs originate from the progressive de-differentiation of well-differentiated NSCLC into sarcomatous like entities.

This hypothesis has found supporting evidence in recently released studies in which genetic and molecular profiling were used to investigate similarities and differences between the different components of PSCs. A recent study used exome sequencing to compare the mutational landscape of well-differentiated and sarcomatoid components in a small series of four PSCs.⁹² Even if limited by the number of cases analyzed, the authors concluded that during evolution, the sarcomatoid component branches very early from the well-differentiated epithelioid component and independently accumulates mutations establishing a profound difference with the original lesions.

We took further these observations showing in vivo that the transcriptional activation of an EMT program drives PSC phylogeny.⁹³ Using Nanostring technology, we performed a deep transcriptional analysis of a series of 32 biphasic PSCs (17 training sets, 15 validation sets). We identified a list of 146 genes whose expression largely marks the phenotypic differences between epithelioid and sarcomatoid components of PSC. Gene Ontology (GO) enrichment analysis demonstrated loss of cell-adhesion and cell-junction properties as well as other epithelial specific features in the sarcomatous components and identified TGF-beta and many TGF-beta-induced transcription factors as upstream regulators of this phenotype. In accordance with previous reports, ECAD, a typical marker of epithelial cancers, emerged as differentially expressed gene and was consistently lost in sarcomatoid cells. Noticeably, from our analysis strongly emerged that the molecular reorganization that sustains the acquisition of

the sarcomatoid phenotype relies on a profound rewiring of the gene expression program. This is driven by a functional switch between epithelial-associated TFs and mesenchymal-associated TFs, thus providing new clues into the molecular events that underline PSCs evolution but also the first formal proves that the activation of the EMT program drives this process.

Clinical Impact of PSC Molecular Profiling

Given the discouraging results with conventional chemotherapy, new therapies are needed to improve the management of PSCs. The recent identification of *MET* exon 14 mutations shed new lights on the unique biology of PSCs and opened the first prospective on PSC-oriented therapy. Here, we discuss on how the recently gained molecular insights into their biology may overturn PSCs therapy in the next years.

While providing confirmation of the close genetic proximity between PSC and NSCLC, these studies also indicate how these lesions harbor precise differences that at least in part may account for the failure of previously attempted targeted therapy in PSC.⁹⁴ For instance, *EGFR* actionable mutations are quite frequent in NSCLC and treatment with TKI is a first-line therapy for *EGFR* mutated patients. Few reports of PSC patients treated with EGFR inhibitors are currently available but thus far a lack of significant and stable response has been observed.^{50,95} *EGFR* mutations in PSC is controversial (0–28% depending on series) but surely inferior to NSCLC.^{81–84,96–98} Furthermore, according to the available information, the number of actionable *EGFR* mutations (p. L858R) is even lower further reducing the rationale for the employment of these drugs in this setting. Besides, the absence of evident response to EGFR inhibitors even in *EGFR* mutated PSCs, seems to indicate that *EGFR* mutations in these tumors may not be an essential driver but rather a secondary event.

KRAS mutations are among the most common alterations detected in non-squamous NSCLC. Together with alterations in *TP53*, *KRAS* mutations are also quite frequent in PSCs with a reported occurrence that range between 15% and 39% depending on series.^{81–85} Mutations in 12 codon are the most frequent even if mutation in codon 61 has also been reported. *KRAS* mutations have been found significantly associated with pure sarcomatoid or with PSC with an adenocarcinoma component.^{82,84} *KRAS* mutations are

predominantly found in PSCs from smokers, and the majority of the alteration detected are transversions, the typical DNA alterations found in smokers' adenocarcinomas.⁸⁴ Prognostic significance of *KRAS* mutations in PSC has been a matter of debate, in particular due to the limited number of cases in the analyzed series that precluded conclusive results. However, we recently showed that *KRAS* mutations alone or in combination with *TP53* mutations were associated with local metastases at recurrence and with a significantly decreased survival probability in a cohort of surgically resected PSCs.⁸⁴ Similarly, Mehrad and colleagues reported a significant correlation of *KRAS* mutations with worse patients' outcome.⁸⁶ We also showed that the presence of *KRAS* mutations significantly correlates with increased PD-L1 expression suggesting a possible correlation, to be further investigated, between these mutations and response to immunotherapy.⁹⁹ These results together with the recent emerging MEK inhibitors may imply a potential value of *KRAS* mutations as relevant predictive markers in orienting PSC tailored treatment. Last but not least, the encouraging preclinical success of *KRAS*-specific inhibitors further consolidate the relevance of these mutations in the managing of these tumors.^{100,101}

MET exon 14 skipping mutations cause stabilization of *MET* protein leading to the constitutive activation of its signaling.⁸⁷ NSCLCs with activating alterations of *MET* (including *MET* locus amplification) have shown remarkable response to small molecules like crizotinib, cabozantinib or capmatinib that target *MET* activity.¹⁰² For the same reason, the presence of *MET* activating mutations in PSCs would qualify a good portion of patients (about 30%) based on the reported mutations incidence^{82,83,87,103} for treatment with these drugs. Preclinical evidence shows that tumor cells harboring *MET* ex14 mutations are responsive to *MET* inhibition, even if co-occurrence of *PI3KCA* concomitant gain of function alterations may partially reduce effectiveness of *MET* inhibition.⁸³ Preliminary clinical data on small series or single case confirmed that *in vivo*, PSC harboring *MET* exon 14 mutations show effective response to *MET* targeting drugs.^{83,104–107}

Even if revolutionary in the desolated PSC treatments landscape, the discovery of *MET* exon 14 mutations and the consequential possibility of directing patients to *MET* inhibitors is limited to a reduced number of patients. Besides, *MET* inhibitors as well as other selective targeting drugs are limited by innate or adaptive resistance keeping the need of new PSC-oriented therapies. The identification of effective therapies for rare cancer like

PSCs poses many challenges and does not fit within the standard design of clinical trials. Thus, alternative strategies like the one of drug re-purposing offer obvious appeal (reduced costs and time) and represent a sustainable strategy for rare cancers. Coherently with this reasoning, we used gene expression profiling data based on human samples as the basis for searching the cMap database¹⁰⁸ containing information of over one million FDA-approved drugs and identified ready-to-use compounds potentially matching the ability of counteracting the PSC-associated gene program. Dasatinib was found as the top scoring drug in this analysis. *In vitro* studies confirmed the effectiveness of this drug in PSC-like cancer cells and its preferential activity for PSC vs well-differentiated NSCLC model.⁹⁶ Dasatinib is a broad-spectrum TKI designed to target among the others pro-oncogenic kinases like *SRC*, *DDR1* and *DDR2*. It has obtained positive results in NSCLC trials and has been registered for clinical use in this setting.¹⁰⁹ Furthermore, consistent evidence indicates that Dasatinib suppresses TGF-beta-mediated EMT in both lung normal and cancer cells preventing insurgence of pulmonary fibrosis and EMT-mediated drug resistance.¹¹⁰

Targetable mutations in PSC are less frequent than in NSCLC with adenocarcinoma histology. However, Fallet et al⁸¹ reported uncommon/rare *EGFR* mutations in 22%, *NRAS* and *PI3KCA* in 5%. Li et al⁸⁵ performed an NGS study evidencing hot spot druggable gene alterations involving *EGFR* (exon 19 deletion) and *EML4-ALK* fusion in sporadic cases. Mehrad et al⁸⁶ evidenced actionable genetic mutations in *EGFR* in 2 out of 23 PSCs (8.7%) and Schrock et al⁸² observed targetable genomic alteration in *EGFR* (8.8%), *BRAF* (7.2%), *erb-b2 receptor tyrosine kinase 2 gene (HER2)* (1.6%), and *ret proto-oncogene (RET)* (0.8%). Of note, no rearrangements in *ALK*, *ROS1* and *NTRKs* were found in the last series.

Finally, Ali et al¹¹¹ disclosed sporadic mutations in *EGFR* (1 case), *MET* (2 cases) and *BRAF* (1 case), *KRAS* (2 cases), *PI3KCA* (2 cases) and 1 *ALK*-rearranged case among 14 PSC using a combined approach with Sequenom Mass-Array and Sanger sequencing and NanoString technology.

By contrast, Nakagomi et al⁹⁵ evidenced prevalent mutations in *TP53* and *KRAS* coupled to Microsatellite instability/Mismatch repair system alteration in one case among four PSCs deeply investigated by NGS.

Several reasons may explain the wide range of incidence of druggable gene alterations in PSC, as follows: a) a selection bias related to the accuracy in diagnosing this unusual histology (i.e., application of morphologic criteria

in biopsy versus resections, lack of specific diagnostic primary antibodies at immunohistochemistry); b) various methodologies in detecting gene alterations, including techniques with a significantly large range of sensitivity; and c) different ethnicities of the reported case series.

Overall, targetable gene alterations are less frequent in PSC than in non-squamous NSCLC, although *MET* and *BRAF* oncogene mutations are relatively more common in this unusual histology.^{82,94}

Interestingly, among acquired resistance mechanisms during treatments with tyrosine kinase inhibitors (i.e., *EGFR* and *ALK* inhibitors) or chemotherapy, histologic “change” from adenocarcinoma to small cell or squamous cell carcinomas have been well demonstrated in *EGFR* mutated (about 10% of cases) and *ALK* rearranged adenocarcinomas. However, activation of epithelial-to-mesenchymal (EMT) transition leading to sarcomatoid “transformation” has been recently reported by Hsieh et al¹¹² in 6 cases of adenocarcinoma (5 *EGFR* mutated, 1 *ROS1* rearranged). The change from adenocarcinoma histology to PSC was often associated with PD-L1 over-expression (83%), *c-MET* gene alterations or *MET* overexpression (5 out of 6 cases), further supporting the activation of EMT phenomenon in tumor cells.

This histologic change has been previously observed in *EGFR*-mutated cell lines of lung adenocarcinoma by Sequist et al,¹¹³ demonstrating that acquired resistance to *EGFR* TKI was sustained by EMT activation with sarcomatoid spindle cell modification at histology and increased expression of vimentin. EMT as mechanism of resistance to TKI is observed in 1% to 10% of cases^{112–114} and sarcomatoid change in the experience of Hsieh et al is observed in 5% of *EGFR*-mutated NSCLC.¹¹²

Xu et al¹¹⁵ reported a case of lung adenocarcinoma resistant to *EGFR* TKI with concurrent acquired *T790M* secondary *EGFR* mutation and sarcomatoid spindle cell occurrence.

Finally, a case of exon 21 L858R *EGFR*-mutated sarcomatoid carcinoma of the lung resistant to icotinib was recently reported.¹¹⁶ Coexistence of *Nkx2-4* mutation was considered responsible of its intrinsic resistance to *EGFR* TKI.¹¹⁶

PSC and Immunotherapy

Immunotherapy by blockade of immune checkpoint pathways like the PD1/PD-L1 signaling has dramatically impacted on therapy of many chemo-resistant cancer patients.^{117,118} Rational exists for the use of immune checkpoints inhibitors also in PSCs, relying on at least

two different assumptions. First, immunotherapy has shown remarkable results in NSCLC improving progression-free and overall survival, causing fewer adverse events than standard chemotherapy in a significant portion of patients.¹¹⁹ Second, recent evidence indicates that the strength of immunotherapy is higher in tumors that like PSC or, more in general tobacco-associated tumors, are characterized by high degree of genetic damage.¹²⁰ Up to now only sporadic reports of single cases on the use of immunotherapy in PSCs are available, but these preliminary data are encouraging and seem to corroborate the employment of immune checkpoint blockade in this setting.¹²¹

Currently, no definitive predictive marker to anticipate response to anti-PD1 or anti-PD-L1 antibody is available. PD-L1 expression in either tumor or lymphocyte infiltrate positive¹²² and tumor mutational burden¹²⁰ have been reported to be positively associated with the strength of immunotherapy response and investigated as potential predictive markers.

In PSCs, several reports have investigated the expression of PD1 and/or PD-L1 to envisage a possible use of these therapies in this setting.^{101,123–133} Although widely employed and approved from different national drug agencies,¹²³ PD-L1 expression is an imperfect predictive biomarker for immunotherapy in lung cancer. PSC tends to show high levels of immunohistochemical expression with PD-L1, even if it is quite difficult to compare the data so far reported in literature in this histology. Indeed, the main problem is related to technical clues related to numerous cut-offs of expression to quote positivity, different primary antibody clones and automated platforms as well as laboratory-developed tests used in scientific works.

A recent paper by Ali et al¹¹¹ showed PD-L1 expression $\geq 1\%$ in 84% out of 44 PSC and 47% of these cases revealed staining $\geq 50\%$ (clone SP263 using BenchMark XT/Ventana platform). Similarly, Nakagomi et al⁹⁵ demonstrated high PD-L1 expression $\geq 50\%$ in all four PSCs analyzed (clone 28–8 using ULTRA/Ventana platform). Wu et al¹²⁴ detected PD-L1 expression in 21 cases (87.5%) of PSC and SUVmax of 17 lesions with PD-L1 expression degree $\geq 50\%$ was higher than that $< 50\%$ and related to *KRAS* mutations. Chan et al¹²⁵ assessed the PD-L1 expression in 713 consecutive NSCLC by four commercially available PD-L1 immunohistochemical assays (22C3, 28–8, SP142 and SP263) evidencing a high PD-L1 expression $\geq 50\%$ significantly associated with PSC ($p < 0.001$) and mutant *KRAS* ($p = 0.005$) also reporting good agreement between 22C2,

28–8 and SP263 primary antibodies. Sim et al¹²⁶ showed high levels of PD-L1 in 8 out of 13 PSC (61.5%) and Yvorel et al¹²⁷ analogously reported high expression of PD-L1 (clone E1L3N, Cell Signaling Technology) in 75% of 36 PSC. In the series of Kim et al¹²⁹ PD-L1 and PD-L2 were highly expressed in PSC (90.2%; 37/41 and 87.8%; 36/41), respectively. Of note, PD-L1 expression in pulmonary PCs was significantly higher in sarcomatous areas than in the carcinomatous component ($p=0.006$). Vieira et al¹³⁰ reported high PD-L1 (clone 5H1) immunoreactivity in 40 out of 75 (53%) PSC, also confirming a significant association with the presence of *KRAS* mutations. High expression of PD-L1 in PSC has been similarly noted in other studies.^{101,131}

The frequency of PD-L1 positive PSC samples is significantly higher than the one observed in NSCLC, coherently with higher presence of CD3+ or CD163+ infiltrating lymphocytes or macrophages observed in these tumors.¹³⁰ Together, these observations encourage the use of immunotherapy in the treatment of PSCs.^{131,133}

Take-Home Messages

- Patients with PSC are generally elderly smoking men with large peripheral mass with rounded margins or endobronchial fleshy polyp. Symptoms are non-specific, as well as serum markers, but giant cell carcinoma may produce G-CSF or beta-HCG leading to paraneoplastic conditions (i.e., fever and gynecomastia, respectively).
- The diagnosis of PSC is based on careful examination of morphologic features on hematoxylin–eosin-stained slides using a light microscope, but ancillary techniques (immunohistochemistry, molecular morphology or even ultrastructure analysis) are very helpful in challenging cases. Extensive sampling and serial consecutive sections may be required to disclose the NSCLC component, especially on small biopsy.
- A diagnosis of possible PSC is acceptable on cytology, cell-block and small biopsy, but definitive confirmation should be made on surgical specimen, according to the last 2015 WHO classification of lung tumors.
- In agreement with the 2015 WHO scheme, PSC encompasses five different histological subtypes, namely pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and blastoma.²⁴
- Sarcomatoid/sarcomatous component in PSC has a monoclonal origin driving from metaplastic changes of the carcinoma, secondary to the activation of a genetic program of epithelial-to-mesenchymal transition.³⁹

- Prognosis of PSC is dismal; surgery remains the mainstay of treatment and the role of neoadjuvant/ adjuvant chemo-radiotherapy is controversial and rarely effective.¹²⁵
- PD-L1 over-expression and *MET* exon 14 skipping mutation are the most important predictive biomarkers for effective targeted therapies in PSC.^{134–136}

Disclosure

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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