# Pulmonary Adenocarcinomas

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# Subtyping and differential diagnosis

**by**

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# 1. Introduction

Pulmonary tumors are the most common neoplasms leading to death in Western civilizations including Germany. The 5-year-survival rate is still below 10%. Pulmonary tumors are of epithelial origin with few exceptions. These epithelial tumors are predominantly malignant and therefore correspond to pulmonary carcinomas. In Central Europe the incidence of these tumors is approximately 60 in 100,000 inhabitants per year. The frequency of occurrence of malignant epithelial pulmonary tumors has reached a plateau in the Western world. In Germany the current number of newly diagnosed cases is 60,000 per year with incidences still increasing in women, the latter correlating with the fact that the number of women who smoke has risen some decades ago. The frequency of occurrence is stagnating in men; in some countries it is even decreasing slightly. It is well known that smoking is the main risk factor for developing a lung carcinoma. The influence of this factor is so overwhelmingly great, that other factors i.e. radon, asbestos, uranium, compounds of chrome, yperite, polycyclic aromatic hydrocarbons or nickel are of nearly no significance.

It takes decades for lung tumors to develop. From a biological view, their development is still incompletely understood and it can be assumed the genesis of these tumors is not only based on a single small group of molecular alterations but rather that each single tumor develops as a result of individually different highly complex patterns of multiple alterations on the level of epigenetics, genetics, proteins und metabolites. This was proven again most recently by sequencing of whole tumor genomes of lung neoplasms. Fortunately, however, there is an array of recurrent alterations in this biological chaos that can be used as targets for therapeutic measures.

Back to morphology: Non-small-cell carcinomas (NSCLC) make up the majority of these neoplasms, about 80% of malignant epithelial lung tumors belong to this group compared to about 20% of small-cell (neuroendocrine) carcinomas (SCLC). The group of non-small-cell carcinomas consists of adenocarcinomas, squamous cell carcinomas, large cell carcinomas (which from the biological viewpoint are most likely a mixture of non-differentiated representatives of the above mentioned two groups), large cell neuroendocrine and sarcomatoid carcinomas as well as mixed species (i.e. adeno-squamous carcinoma) and some rare tumor types. Furthermore carcinoids as well as the group of salivary gland tumors have to be considered regarding epithelial neoplasms of the lung (see table 1).

With a percentage of about 60%, adenocarcinomas make up the largest subgroup of non-small cell carcinomas of the lung. Pulmonary adenocarcinoma alone thereby has to be considered the most frequent tumor in men in the Western world leading to death and ranks second regarding the frequency of lethal tumors in women. It is more fatal than colon

cancer (in both sexes) as well as prostate cancer (in men). To point out the extraordinary importance of these tumors, one has to point out that annually far more Germans die of an adenocarcinoma of the lung than of all lymphomas, leukemias, brain tumors and sarcomas together.
Prediction of prognosis as well as prediction of the response to different therapeutic regimens (surgery, radiation, chemotherapy) is of high importance for therapy planning in almost every tumor entity. Tumor staging is the most important factor in this regard. Recently a new staging system of lung carcinoma was proposed on the basis of a large international data set assembled by the IASLC. This system is to be used uniformly to classify all types of lung cancer (including small-cell carcinomas and carcinoids).

A large variety of additional molecular factors have been proposed for prognostic evaluation as well as for response prediction prior to a specific treatment during the last years. However, except very few molecular factors (EML4-ALK translocations, EGFR mutations), all of them failed to enter every-day clinical practice due to a range of reasons. Important obstacles in this regard are an insufficient validation status for many of these biomarkers as well as the fact that most of these tests are too expensive or too complex to be of used in every-day clinical practice.

Apart from molecular factors, conventional morphologic factors like histological subtyping and histological grading are of utmost importance for the estimation of patient prognosis in a variety of solid human tumors and therefore has entered clinical decision making in high-frequency tumor entities like breast and prostate cancer. Since a great deal of information has been gathered in this field in pulmonary adenocarcinoma over the last years, in the following we will give a short review about those novelties.

# 2. The lepidic lesions

## Introduction

“Lepidic” refers to growth of atypical, cuboidal, adenoid cells alongside preexistent alveolar walls. The term ‘lepidic lesions’ comprises patterns of growth of epithelial cells formerly known as bronchiolo-alveolar type of growth. Since the term ‘bronchiolo-alveolar’, however, in the last years has been used beyond its definition and an array of lesions which show a quite different biological behavior were labeled with this term, the IASLC/ATS/ERS recommend no further usage of it. The origin of the term ‘lepidic’ itself is a controversial subject. It is defined as ‘covered by a scabby layer’ by the American Heritage Medical Dictionary which might correspond to the ragged “scaly” way the lepidic alveolar surface-coverage sometimes looks like.

With very few exceptions, lepidic lesions are defined as genuine neoplastic, however this group of lesions also comprise precursors in which the malignant potential cannot be finally assessed for each individual case. E.g. cuboidal metaplasia in the context of interstitial lung diseases are part of these precursors as is mucinous metaplasia in the context of congenital pulmonary malformations (CPAM) as they occur in children occasionally.

However, the actual consensus sequence of tumor development in lepidic pulmonary neoplasms consists of 3 tumor types: atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), minimal invasive adenocarcinoma (MIA), and finally lepidic predominant conventional adenocarcinoma which is dealt with later in the section on the frankly invasive adenocarcinomas.

In CT scans this group of tumors shows quite a distinct morphology dominated by ground glass opacities. Not surprisingly, this frequently leads to difficulties in the delineation of these tumors from inflammatory alterations of lung parenchyma.

## Atypical adenomatous hyperplasia (AAH)

In most instances atypical adenomatous hyperplasia cannot be visualized by radiological methods and is therefore usually detected as an incidental finding in resected lung tissue of patients who were treated for an invasive adenocarcinoma. However, it occasionally also occurs in resected tissue of patients who suffered from other lung diseases. AAH is a clonal lesion of adenoid cells defined by cytomorphology and growth pattern which can doubtlessly be a precursor lesion of adenocarcinomas. However, reliable data regarding its likelihood of progression are not available.

AAH is histomorphologically defined as atypical polygonal cells coating the alveolar walls in a lepidic fashion. The cells which may resemble type II pneumocytes, Clara cells or bronchiolar epithelium show mild to moderate cellular atypia and are of a circular, cuboidal or low prismatic shape. Small indentations respectively gaps can be typically found between two neighbouring cells (so-called hobnail phenomenon). Intranuclear inclusions are frequently seen. Due to a lack of reproducibility, a classification in low- and high grade lesions is not recommendable at present. From a cytomorphological viewpoint there is a continuum to the morphology of AIS. AAH lesions reach a maximum diameter of ≤5mm by definition. This size criterion is crucial in the diagnosis of AAH, we would consider the diagnosis of AIS in patients with smaller lesions only in very rare cases showing massive cellular polymorphism. It goes without saying that the diagnosis AAH can only be made if the lesion has been completely resected and sampled. Normally AAH expresses CK7, TTF1 and Napsin. The proliferative activity is variable, but mostly very low (below 5%). Immunohistology is of no use in the

diagnosis of these lesions. Apart from AIS, especially metaplasia with reactive atypia in inflammatory lung diseases is to be considered in the differential diagnosis. In general, one has to be very cautious with the diagnosis AAH if there is an inflammatory background.

## Adenocarcinoma in situ (AIS)

AIS is a neoplastic lesion with an exclusively lepidic pattern of growth and *without* any invasive focus. Designation of these lesions as 'in situ' is based on data proving that these tumors, if they are completely excised and unifocal, show a 100%-survival rate. The term AIS comprises tumors designated as non-mucinous bronchiolo-alveolar carcinomas (and some rare tumors from the group of mucinous BAC, as well, see below) by the former WHO-classification. The overall size of these tumors is >5mm and ≤3 cm by definition. At present, no sufficient data is available about the biological behavior of tumors showing an AIS-like morphology and a diameter of more than 3 cm. Therefore, for the time being these tumors have to be summarized in the group of invasive neoplasms and should be designated as predominant lepidic adenocarcinoma (see further below). In addition, in these cases it is recommendable to add a respective comment in this regard. As AAH and non- mucinous AIS show a continuum of cellular atypia it is difficult if not impossible to differentiate between both lesions only on the basis of cytology. Accompanying septal fibrosis without an associated inflammatory interstitial infiltrate, which can nearly always be observed, is an important criterion for the diagnosis of these lesions. Formation of a central scar can often be seen. The outer boundaries of these lesions are usually relatively sharp. No stromal, vascular or pleural infiltration can be found by definition. These tumors mustn't show papillae, micro-papillae and intra-alveolar tumor cells. In most cases AIS is a solitary tumor and very rarely may comprise several independent primary tumors; multifocal tumor growth usually excludes the diagnosis of AIS. In some cases differentiation between lepidic growth in AIS and micro-papillary growth (which is not a feature of AIS) is difficult, especially in the case of a somewhat "serrated" epithelial configuration. This also applies to the differentiation between AIS and papillary growth (pulmonary morphology still maintained or already secondary structure?). This matter will be discussed for the respective patterns in this tutorial later. AIS is classified according to the latest consensus proposal by the IASLC/ATS/ERS as pTis. The diagnosis of AIS might be rendered on the basis of high quality frozen sections with a certain level of confidence. Occasionally difficulties arise in the delineation of minimally invasive adenocarcinomas (see below), however, this differential most likely is of minimal clinical relevance since both entities show excellent survival times.

Apart from the frequently occurring non-mucinous variant of AIS, which is diagnosed in approximately 1 in 100 patients with resected adenocarcinomas in our cohort, a mucinous variant of AIS has also been described. These tumors show subtle hyperchromatic, still basally located nuclei and apical mucin; goblet-cells might also occur. This tumor entity is NOT identical to the former mucinous bronchiolo-alveolar carcinomas since the latter usually shows multifocal growth as well as micropapillae and invasion, all three features are not compatible with the diagnosis of AIS**.** In contrast, these neoplasms form the entirely new tumor entity of mucinous adenocarcinoma (see

further below). We have not seen a purely mucinous AIS up to now (even in our retrospective cohorts comprising far more than 1000 NSCLC).

Immunohistologically both tumor entities, the mucinous as well as the non-mucinous variant are positive for CK7, Napsin and TTF1, however the non-mucinous variant is said to show only infrequent expression of Napsin. Proliferative activity can be very low in some cases (as low as 1-2%).

The differential diagnosis includes reactive cellular atypia in inflammatory lung diseases. Inflammatory cells are only found in small quantities in AIS. In case of an accompanying inflammatory infiltrate the diagnosis of AIS has to be made very cautiously. AAH distinguishes itself from AIS by its size (>5mm) and by somewhat soft criteria in cytomorphology. MIA and lepidic predominant ADC show invasive foci (see there). Pulmonary metastases with purely lepidic growth do practically never occur.

## Minimally invasive adenocarcinoma (MIA)

The minimally invasive adenocarcinoma is, as well as AIS, a new tumor entity which is not listed by the WHO classification (2004) but which nevertheless should be considered for diagnosis according to the IASLC/ATS/ERS-consensus. Cytomorphologically, the mucinous and non-mucinous variants of these tumors comply with AIS forms. The only criterion for distinction of these two entities is the presence of microinvasion. Differentiation between these two tumor entities and frankly invasive adenocarcinomas has to be established with certainty since the former in contrast to the latter show an almost 100% survival-rate after complete resection. To be classified as MIA, a tumor should have a size of ≤3 cm. Larger tumors are automatically classified as conventional invasive adenocarcinomas (with a comment, see the part on AIS). To meet the criteria of MIA, these predominantly lepidic neoplasms have to show invasive foci with a diameter of ≤5 mm. In case of several invasive foci the diameters are not added but the largest diameter has to be used for classification. Therefore, a tumor featuring 3 invasive non-connected foci of 4 mm diameter each still meets the criteria of MIA. The invasive focus can be of acinar, papillary, micropapillary, and solid architecture. It can also consist of single cells in myofibroblastic stroma. Regarding papillary/ micropapillary growth patterns it should be noted that a stroma invasion in the narrower sense has not necessarily to be established. Here the existence of the respective growth patterns in itself might be regarded as “invasion”. Acinar-solid microinvasive foci are often found in the neighbourhood of central scar areas in AIS-like tumors. Sometimes differentiation of enclosed, residual or collapsed alveolar spaces from invasive foci can cause problems (see cases).

By definition, MIA do not show vascular or pleural infiltration and tumor necrosis. These

tumors are solitary. Multifocality excludes the diagnosis, if not several synchronic primary tumors are present. MIA according to the IASLC/ATS/ERS consensus should be classified as pT(mi). Whereas non-mucinous MIAs are diagnosed occasionally (in our cohort again one in a hundred patients with lung adenocarcinomas who have undergone surgery), the mucinous variant of these tumors is extremely rare. We have never seen such a tumor.

The immunophenotype of both variants correspond with the one of AIS. Delineation of MIA from AIS is sometimes difficult. However, since both tumors show a biologically comparable behaviour from a pragmatic clinical viewpoint the definite categorization is not crucial. Lepidic predominant adenocarcinomas are distinguished from AIS by the size of the invasive focus (>5mm).

# 3. Conventional invasive adenocarcinoma

## Lepidic growth

The lepidic growth pattern in pulmonary adenocarcinomas corresponds to the one of AAH, AIS and MIA. Characteristics of this growth pattern can be summarized as follows: Single layered proliferates of usually only mildly to moderately atypical, roundish or cuboidal cells with hyperchromatic nuclei and quite often with nucleic inclusions coating the alveolar walls. Septa are widened. Sometimes a certain coarsening of lung parenchyma structure is seen which is, however, in principle completely intact. We recommend additional staining of elastic fibres (EvG) for the assessment of possible secondary structures and for the evaluation of potential destruction of the basic alveolar architecture.

For the differentiation of lepidic predominant tumors from AIS/MIA an invasive focus >5mm, a size >3cm or vessel/pleura infiltration is to be requested. Lepidic patterns are often found in combination with acinar tumor differentiation as well as in all kinds of mixed types. With roughly 20% of adenocarcinomas showing predominant lepidic growth it is the third most frequent predominant pattern. The most frequently encountered problems derive from the differentiation from papillary and acinar tumors. Exact assessment of this pattern is not a difficult task for experienced pulmonary pathologists but is associated with more difficulties for less experienced colleagues.

## Acinar growth

Acinar differentiated tumors form glandular structures which usually show a small glandular/ductal configuration. The neoplastic glandular structures are irregularly angulated and in parts branched in a complex way. However, the occurring forms of acini are extremely diverse ranging from small microacinar structures to large branching complex ones. Cribiform areas are summarized under acinar growth. Cord-like arranged tumor cells with an acinar 'polarity' should also be considered as acinar. Cytomorphologically any imaginable differentiation is possible. There are tumors with massive nuclear polymorphism and tumors showing completely bland monomorphic nuclei. In some of the tumors clear or vacuolar cytoplasm is found whereas others have a densely eosinophilic or basophilic cytoplasm. Sometimes the glandular cells and lumina contain mucin. Cytomorphology has no impact on classification. Especially in mildly autolytic samples the acinar growth pattern is sometimes difficult to detect as "pseudopapillary structures" are prevalent in these cases. Acinar growth patterns frequently come along with solid and lepidic growth patterns and are present in a large variety of different growth pattern combinations. With 35% of cases the acinar growth pattern is the second most common predominant pattern. Difficulties may arise in the differentiation from lepidic and solid growth patterns. As long as "acinar" basic structures with cell polarity can be detected the growth pattern is to be classified as acinar even if the lumina seem to be compressed or even lost by tumor proliferation. A cribriform growth pattern is to be classified as acinar, too. Altogether, a moderate to good agreement in the classification of this pattern can be reached by experienced pulmonary pathologists as well as by less experienced colleagues.

## Papillary growth

The recognition of real papillary structures with a central, often vessel containing stromal core is the key to the identification of papillary tumor differentiation. Width and length of the stromal core is very variable in lung cancer. Accompanying micropapillary folding on the surface occur but is, in small quantities, no reason for a classification as micropapillary growth. If papillary "non-invasive" structures are found in lepidic-coated distended alveolar spaces and in acinar type structures the growth pattern has to be classified as papillary. The occurrence of stromal desmoplasia is not necessary in this context. Papillary growth is sometimes accompanied by psamomma bodies. Cytologically these tumors are very variable. The spectrum ranges from highly pleomorphic neoplasms which morphologically remind of serous carcinoma to forms with a quite monomorphic cell picture, the latter not seldom resembling the cellular morphology in thyroid cancer. Cytology has no impact on the classification of these tumors. A papillary growth pattern is most common in mixed forms of adenocarcinomas. Delineation of papillary growth from all other growth patterns is quite difficult and misinterpretation is common. For differentiation of lepidic from papillary growth a decision has to be made whether real stroma papillae or cross cut septa are seen (mostly papillary). In the differentiation between papillary and acinar tumors irregular

branched and anastomosed acini often cause difficulties (mostly acinar). Delineation from micropapillary growth (mostly papillary) is complicated since micropapillae commonly occur on the surface of papillary structures. Predominant papillary tumor differentiation in our data sets is rare (5%). The corresponding numbers from international studies, however, vary strongly and are sometimes as high as 30% which points on the necessity to establish a more precise definition of this pattern. Conformity in assessment of this pattern is moderate for pulmonary pathologists, but relatively low for pathologists without a special expertise in pulmonary pathology.

## Micropapillary growth

Development of genuine, by definition stromaless micropapillae often resulting in intra-alveolar tumor cells/tumor cell accumulations is the basis for a classification of a growth pattern as micropapillary. Sometimes ring-shaped glandular structures might occur in alveolar spaces, as well, this growth pattern also classifies as micropapillary. Frankly invasive growth in the conventional sense is not necessary for a classification of a pattern as micropapillary. Recent studies with 3D reconstruction of serial sections could show that the micropapillary pattern consists of epithelial proliferates interconnected in a netted way which also show an utterly subtle stroma. In the conventional HE slide the impression of stromaless micropapillae is created by orthogonal sectioning through these structures. Tumors with micropapillae in distended lepidic coated alveolar spaces or within acinar basic structures are also classified as micropapillary. Stroma desmoplasia is not a criterion and might or might not occur. Psammoma bodies are sometimes observed. Histomorphologically this growth pattern is reminiscent of micropapillary tumors which occur in other organs (for example breast and colon). Cytomorphologically, a wide range of different cellular appearances might be present ranging from bland monomorphic cells up to strongly polymorphic individual intra-alveolar cells. Micropapillary predominant tumors are the rarest tumor type (3%) in our cohorts. When such a predominant growth pattern is present, however, metastasis to regional lymph nodes has occurred in > 75% of cases at the time of surgical resection. The micropapillary growth pattern is most prevalent in mixed adenocarcinomas. Classification of this pattern is not easy and quite often there's confusion with the papillary type (see above). When "serrated" tumor growth alongside alveolar septa or along neoplastic acini is seen, it is difficult to make the separation from the lepidic/acinar growth pattern. Such a growth pattern might potentially point on micropapillary structures "in statu nascendi". Therefore, when serrated morphology is extensive we classify these tumors as micropapillary since in our cohort these tumors have a considerably poorer prognosis when compared to "conventional" lepidic/acinar adenocarcinomas. Dissociated tumor cells in autolytic tumors must not be confused with micropapillary growth. Conformity in assessment of this pattern is moderate in pulmonary pathologists and relatively low in pathologists without specific expertise in this field.

## Solid growth

Cohesive cell agglomerates in a nest-like configuration without acinar polarity are the hallmark of the solid growth pattern. Cribiform areas, however, are part of the acinar growth pattern. Cytologically tumors of this pattern are often very variable. This comprises, for example, clear cell areas as well as tumor areas with dark eosinophil or basophilic cytoplasm. The nuclei tend to show strong polymorphism. In order to establish the diagnosis of a solid adenocarcinoma in an exclusively solid tumor (this problem usually occurs more often in biopsy material than in resected tumors) detection of 5 PAS-positive cells in two neighbouring high powerfield views (HPF) is required. Squamous cell carcinoma has to be ruled out by the lack of intercellular bridges and keratinisation. Differentiation from solid tumors with a neuroendocrine cell morphology must be made, as well. When in doubt, immunohistochemistry for exclusion of carcinoid/LCNEC is required. The solid growth form is the most common predominant pattern (37%) in pulmonary adenocarcinomas. When occurring in combined tumors it is often accompanied by the acinar pattern. Differentiation between the solid growth form and other growth patterns presents no particular difficulty. Overall, this pattern is easy to recognize by both pulmonary pathologists and colleagues less experienced in the field of lung pathology.

## Final remarks

Classification of pulmonary adenocarcinomas according to the predominant growth pattern is reliably possible and growth patterns are a strong stage-independent predictor for survival. A study carried out by us on 100 pulmonary adenocarcinomas in which we evaluated the interobserver variability in the designation of the predominant growth pattern yielded K -values ranging between 0.44 and 0.72 for pulmonary pathologists. These K -values are comparable to K-values published for established grading-systems in other tumor entities (such as Gleason grade or Elston-Ellis grade). Pathologists without a specific expertise in pulmonary pathology had K -values which initially were substantially worse (0.38-0.47). These K-values, however, could be elevated to K-values achieved by pulmonary pathologists by training sessions which subsequently motivated us to develop this tutorial. Intraobserver variability was quite low in the aforementioned study. Unfortunately, as could be somehow expected, more tissue slides led to a higher variability in pattern assessment. This points on a certain conflict between accurate classification (embed much tissue) and reproducibility (embed less tissue). Up to now no requirements regarding processing of tissue have been published. In this context, we recommend embedding at least one central

tumor lamella in the region of the largest diameter *in toto*. According to our experience this approach reflects distribution of patterns within a tumor more precisely (for example central solid and peripheral lepidic) when compared to non-oriented embedding of a tissue block per cm of tumor diameter.

# 4. Special forms of invasive pulmonary adenocarcinomas

## Introductory remarks

Compared to the WHO classification in 2004 the special forms of pulmonary adenocarcinoma have been revised significantly. Some new entities have been defined, among them the invasive mucinous as well as the enteric pulmonary adenocarcinoma. Those tumors which were formerly named mucinous adenocarcinomas have now been renamed as colloidal adenocarcinomas whereas the entity of fetal adenocarcinoma remains essentially unchanged. The very rare entity of cystadenocarcinoma has been eliminated, these tumors are now summarized in the group of colloidal adenocarcinomas. Furthermore the distinct entity of signet ring cell carcinoma was eliminated, as well, it is now recommended to do the classification of the respective adenocarcinomas according to pattern and to refer to the signet ring cell element in an addendum. However, regarding this entity it is not finally clear whether this categorization should be maintained since distinct molecular alterations (frequently occurring EML4-ALK fusions) are said to be associated with signet ring cell morphology. Clear cell carcinoma is another entity which was legitimately eliminated since the group of tumors formerly classified as being clear cell carcinomas are presumably a heterogeneous mixture of clear cell squamous-cell carcinoma and adenocarcinomas with clear cell morphology. The respective clear cell adenocarcinomas are now classified according to their pattern with no need to refer to their clear cell morphology.

## Invasive mucinous adenocarcinoma

Most tumors formerly designated as mucinous bronchioloalveolar carcinomas are part of this novel entity. These tumors show a predominantly lepidic growth pattern. However, they invariably also show papillae and/or micropapillae and invasive acinar structures are also frequently present. In some tumor areas the basic structure of the lung is destroyed. The tumor cells are columnar, with elongated hyperchromatic nuclei. Tumor cells show significant intracytoplasmic, mostly apically located mucus. Tumor growth is frequently multifocal with indistinct tumor boundaries. From a morphological, immunophenotypic and molecular point of view, these neoplasms clearly form a separate tumor entity. This distinct

growth pattern is rarely associated with growth patterns reminiscent of conventional adenocarcinoma. Combinations with a colloidal growth pattern (see below), however, are quite frequent. In such a setting the predominant pattern defines the tumor entity. By immunohistochemistry these tumors frequently show an expression of CK20 and CDX2. Usually CK7 is also expressed. TTF1 and Napsin as well as SPA are often negative. This tumor entity regularly shows KRAS mutations. Invasive mucinous adenocarcinomas tend to disseminate by way of airborne intrapulmonary spread (also bilateral). Lymph node and distant metastases rarely occur. Like other lepidic predominant neoplasms these tumors appear radiologically as ground glass opacities (GGO), therefore these tumors are sometimes difficult to differentiate from inflammatory infiltrates in CT scans.

## Colloidal adenocarcinoma

Colloidal adenocarcinomas as defined in the current classification correspond to the former mucinous adenocarcinomas. These tumors grow by overtly destroying lung parenchyma and under formation of huge concentrations of mucus. Within these lakes of mucus single or grouped dispersly distributed ‘floating’ tumor cells/cell complexes are usually seen. Cytomorphologically these tumors are typically quite bland with only low polymorphism of the slightly hyperchromatic nuclei. When such a growth pattern is predominant the respective tumor can be classified as colloidal adenocarcinoma. This tumor entity now also comprises the former mucinous cystadenocarcinomas. Immunohistologically these tumors often show a pulmonary phenotype with expression of CK7, TTF1, Napsin and SPA.

## Fetal adenocarcinoma

This extremely rare variant of pulmonary adenocarcinomas is composed of histological structures reminiscent of the fetal lung. It is composed of glandular and tubular structures of glycogen-rich cells with no cilia attached. The perinuclear glycogen-vacuoles are somewhat reminiscent of endometrioid tumors. Roundish morula which consist of polygonal cell elements with often eosinophilic and slightly granular cytoplasm are frequently seen. Clear cell differentiation has been described. Some case reports described that tumors with such a morphology might occur in combination with conventional adenocarcinomas. The differential diagnosis of fetal adenocarcinoma includes pulmonary blastoma, however, in the latter the existence of sarcomatoid, primitive-blastomatous stroma is usually obvious.

### Enteric adenocarcinoma

Enteric adenocarcinoma of the lung is a newly established rare pulmonary tumor entity. These tumors are morphologically and immunophenotypically indistinguishable from adenocarcinomas of the intestinal type. Their columnar tumor cells usually show a pseudostratified configuration and have elongated hyperchromatic nuclei accompanied by a basophilic cytoplasm. Tumor cells frequently form large glandular and cribriform nests. Areas of so called “dirty necrosis” are common. To make this diagnosis, at least one enteric differentiation marker should be positive (CDX2+, CK20+, MUC2+). A pulmonary adenocarcinoma might be classified “enteric” if more than 50% of the tumor shows the respective morphology (the reason why for this specific tumor entity the rule of predominance has been abandoned is unclear to us). In most cases “enteric” tumor areas are accompanied by conventional adenocarcinoma growth patterns. Histomorphologically as well as immunophenotypically these tumors cannot be distinguished from colorectal carcinomas if they occur in the pure form (extremely rare, we have seen one case). Therefore, before making this diagnosis, a colorectal carcinoma metastatic to the lung has to be excluded with certainty by our clinical colleagues.

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