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Pulmonary mucinous adenocarcinomas: a clinicopathologic series with emphasis on the prognostic significance of spread through alveolar spaces, and presence of solid growth component

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Abstract

Background: Mucinous adenocarcinoma is often considered a relatively poor prognostic group among adenocarcinomas of the lung and has a high rate of pulmonary recurrence. Pathologic parameters predicting poor outcome have not been extensively studied, including the presence of spread through alveolar spaces (STAS).

Methods: We retrospectively studied time to lung recurrence and time to distant metastasis in 30 mucinous lung tumors, in relationship to histologic parameters, including spread through alveolar spaces, tumor size, invasive size, % invasive size, growth pattern (solid or cribriform, acinar, papillary, micropapillary, and lepidic), type of mucin-producing cell, and TTF-1 positivity.

Results: Median follow-up was 40 months. There were 7 patients (23%) with lung recurrence (mean 22 months) and 7 (23%) with distant metastases (mean 3.7 months). Columnar / goblet cell type was inversely correlated with TTF-1 expression ($p = 0.01$). The only pathologic parameters associated with outcome were STAS for lung recurrence ($p = .005$) and solid/cribriform growth (≥ 20% of tumor) for distant metastasis ($p = 0.003$).

Conclusions: Mucinous adenocarcinomas of the lung are similar to non-mucinous prognostically, in that STAS and solid growth are poor prognosticators, for local and distant recurrence, respectively. The growth patterns of mucinous adenocarcinomas should be reported similar to reporting of non-mucinous adenocarcinomas.

Background

Mucinous adenocarcinomas of the lung account for approximately 10–15% of lung adenocarcinomas and have been reported to portend a poorer prognosis than non-mucinous adenocarcinoma (Cai et al. 2014; Qu et al. 2015; Russell et al. 2011; Travis et al. 2013), however, a recent study has shown that there is no survival difference if adjusted for stage. Compared to nonmucinous adenocarcinomas, mucinous carcinomas have a high rate of local recurrence in the lungs. (Shim et al. 2015)

Mucinous adenocarcinomas have a variety of histologic patterns, and may coexist with non-mucinous areas in combined tumors. It is unclear how variations in architectural patterns typically described for non-mucinous adenocarcinomas affect the prognosis of mucinous adenocarcinomas. (Xu et al. 2013; Kamata et al. 2016; Watanabe et al. 2013) A pure mucinous histologic pattern without non-mucinous elements is associated with lower stage and better prognosis than mixed tumors. (Righi et al. 2016) However, the relationship of histologic pattern of mucinous adenocarcinoma and outcome has not been studied in detail.

Mucinous adenocarcinomas are generally recognized to show a low rate of reactivity for TTF1, as goblet cells are negative for TTF-1 in contrast to pneumocytes and

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Clara cells. However, variations and mixed patterns are frequent in adenocarcinoma, and a strong correlation between mucinous and nonmucinous cells and TTF1 staining patterns has not been established in mucinous adenocarcinomas. (Tsuta et al. 2006; Wu et al. 2013) In general, absent TTF1 reactivity is associated with a more advanced clinical stage and a larger tumor size, if mucinous and nonmucinous tumors are studied together. (Zhang et al. 2015)

Tumor spread through alveolar spaces ("STAS", alternately "aerogenous metastases" or "small cluster invasion") has been linked to poorer clinical outcomes, including higher rates of lymphatic involvement and lymph node metastases (Kawakami et al. 2009), and higher rates of recurrence (Onozato et al. 2013). Recently, STAS has been included as a type of invasion in the 2015 WHO classification of lung tumors. Although considered to be more common in mucinous adenocarcinomas than in nonmucinous tumors, the frequency and significance of its presence specifically in the mucinous subset has not been investigated.

The objective of our study is to correlate histologic features, including presence and type of STAS, architectural growth patterns, percent of invasiveness, mucin cell type, and TTF1 reactivity, with clinical outcome in a series of mucinous adenocarcinomas.

Methods

Case selection

Pulmonary adenocarcinomas resected from 2003 to 2014 were retrospectively reclassified as non-mucinous invasive adenocarcinoma, colloid carcinoma, mucinous adenocarcinoma-in-situ, minimally invasive mucinous adenocarcinoma, or invasive mucinous adenocarcinoma (WHO 2015 reference). Tumors meeting criteria for mucinous adenocarcinoma (in-situ, minimally invasive, or invasive) were included in the study. Tumors classified as "colloid carcinoma", now considered a variant of invasive adenocarcinoma, were included in the study due to significant histologic overlap with "mucinous adenocarcinoma".

Definition of "mucinous"

As no standardized definition for mucinous adenocarcinoma of the lung has been established, "mucinous" was defined in this study as a mucin-producing adenocarcinoma (presence of airspace mucin pools) with intracellular mucin in at least 50% of the tumor cells. Although tumors with a predominant solid growth pattern of mucin-producing cells are now classified as nonmucinous poorly differentiated adenocarcinoma, tumors with a solid component comprising < 50% of the overall tumor architecture were included provided > 50% of the tumor growth consisted of acinar or lepidic growth of mucin-producing (intracytoplasmic) mucin.

Classification of tumor and invasive size

Tumor size included the entire lesion, invasive and non-invasive were recorded used a conventional ocular micrometer. The largest diameter of the tumor was divided into < 2, 2–5, and > 5 cm size categories. The largest invasive component was divided in < 1, 1–2, and > 2 cm size categories. The degree of invasion was also characterized as absent, < 50%, and 50% or greater when measured by linear dimension in the slide in the slide with maximum diameter.

Classification of histologic characteristics

Tumors were classified according to predominant mucin-producing cell type, where mucin production was confirmed with PAS and mucicarmine stains. Tumors were classified as either showing predominantly cuboidal mucin-producing cells with eosinophilic cytoplasm, with no or a minor component of interspersed goblet cells and sometimes showing a fine brush border, or alternately showing a predominance of columnar mucin-producing cells with clear cytoplasm (goblet cells). In the former, most of the tumor cell cytoplasm contained mucin whereas the latter showed apical mucin and prominent PAS staining of the luminal surface. (Fig. 1a-d).

Tumors were also classified similarly to non-mucinous adenocarcinomas into lepidic (in situ), acinar, papillary, micropapillary and solid types (Fig. 2a-d). The presence of signet ring cells as a type of solid growth was also noted. Colloid was defined as airspace expansion by mucus with entrapped tumor clusters, without significant lepidic spread. Tumor nests in colloid carcinomas were not considered STAS, which by definition occurs within normal airspaces. Tumors with 0 or < 20% solid or solid cribriform growth were considered group 1; tumors with 20% or more solid or solid cribriform growth were considered group 2.

The presence of STAS was classified as any tumor nests, islands, tubules, micropapillary tufts, or single cells floating freely within alveolar spaces outside and distant from the egde of the tumor not attached to the alveolar walls (Fig. 3). Clusters within 0.5 mm of the tumor edge was graded as type 1 STAS, whereas clusters beyond 0.5 mm of the tumor edge and present in ≥2 low magnification (2.5 mm diameter) fields were designated as grade 2.

Reactivity to TTF-1 immunohistochemical stain was classified as absent (0), limited to scattered cells with no areas of > 10 contiguous cells staining (1), and areas of diffuse staining > 10 cells contiguously). Care was made to distinguish pre-existing pneumocytes in areas of lepidic growth.

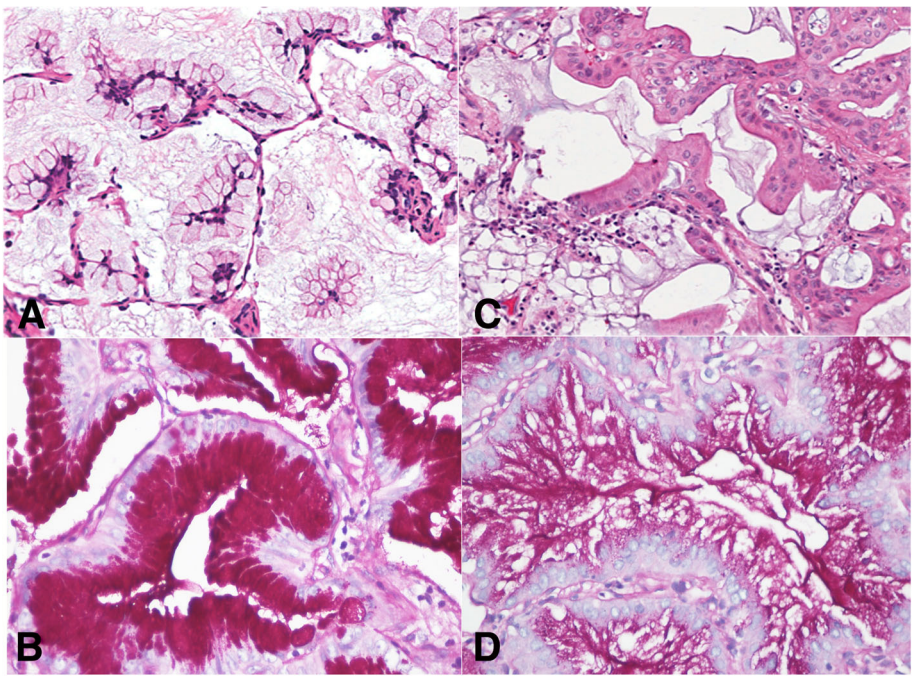

Fig. 1 Types of tumor cell. **a**. Columnar cells with cytoplasmic clearing. **b**. PAS (with diastase pretreatment) demonstrates diffuse cytoplasmic staining with basal nuclei. **c**. Cuboidal cells with eosinophilic cytoplasm. **d**. PAS/diastase shows apical and brush border mucin with extravasation into glandular lumen

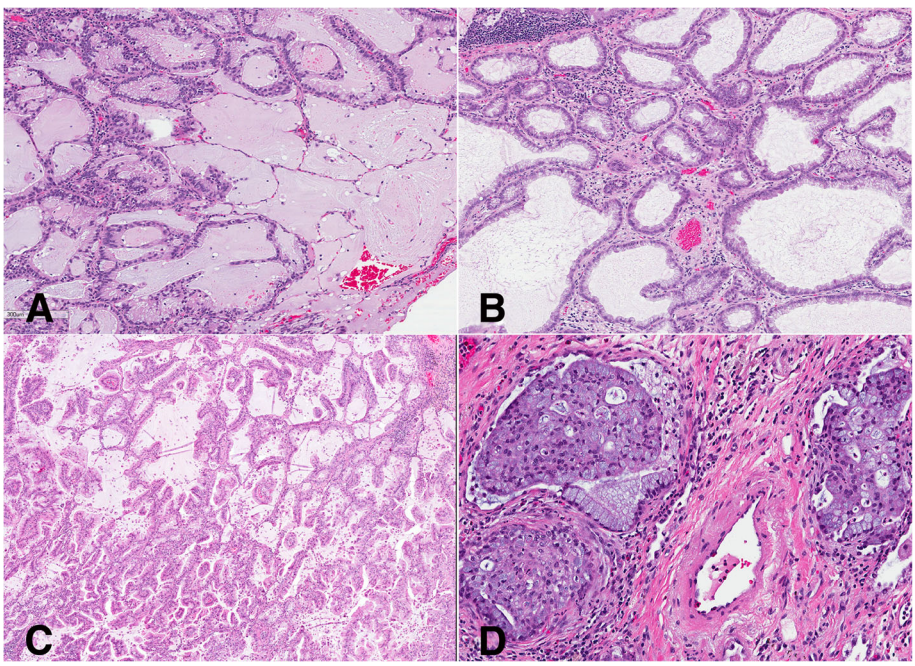

Fig. 2 Patterns of tumor growth. **a**, lepidic; **b**, acinar; **c**, papillary and acinar; **d**, focally solid

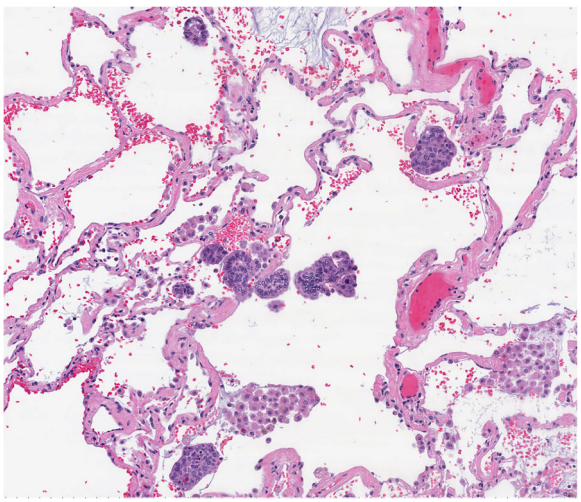

Fig. 3 STAS. The nests are floating inside airspaces and are distinguished from lepidic implants

Clinical parameters

Electronic medical records were utilized to track overall survival, disease specific survival, subsequent lymph node metastases, distant metastases, and tumor recurrence (defined as any subsequent tumor involvement outside of the initial lobe).

Statistical analysis

The proportion of invasive component, size of invasive component, size of solid invasive component, presence of STAS, TTF1 positivity, mucin cell type, and presence of histologic subtypes other than solid were correlated with outcome via Kaplan-Meier curves with log-rank statistic (JMP software, Cary, NC). Censors were set for two times points with statistics run independently: time to distant recurrence; and time to lung recurrence. Because of the low rate of deaths due to disease, survival data were not calculated (no parameters were significant).

Results

A total of 30 cases were included, representing 9% of all resections of pulmonary adenocarcinomas from 2003 to 2014. (Table 1) 17 patients were female (mean age 63) and 13 cases were male (mean age 71), with a F:M ratio of 1.3:1. Tumor size ranged from 0.6 to 8.2 cm. All tumors were treated and diagnosed in a single institution and were discussed in multi-disciplinary conference, with radiological and clinical evaluation and assumption of a lung primary tumor.

Percentage of invasion ranged from entirely lepidic to entirely invasive. 5 cases showed a component of solid non-cribriform growth (% solid ranged from 18 to 50%). The proportions of tumors with solid cribriform, papillary, micropapillary and acinar subtypes are presented in Table 2.

Table 1 Clinicopathologic features, resected mucinous adenocarcinomas ($n = 30$)

Gender (F:M)	17:13
Age, years (mean ± SD)	F: 63 ± 10
	M: 71 ± 6
	($p = .02$)
Invasive adenocarcinoma > 5 mm	25 (93%)
Entirely lepidic or < 5 mm of stromal invasion	5 (17%)
Reclassified (size)[a]	3 (10%)
Reclassified (STAS)[a]	2 (7%)
Entirely invasive	5 (17%)
Columnar cell predominant	14 (47%)
Cuboidal cell predominant	16 (53%)

[a]. Reclassified as invasive from the former WHO classification
STAS = spread through alveolar spaces

Two tumors included in the study were classified as "colloid carcinoma" and 28 cases classified as "invasive mucinous adenocarcinoma". Five tumors had colloid areas but other areas with lepidic spread typical of conventional mucinous adenocarcinomas. Although 5 cases showed either entirely lepidic architecture or less than 0.5 cm of invasion, these cases were all classified as invasive mucinous adenocarcinoma due to the size ($n = 3$) or due to the presence of STAS ($n = 2$). Eight cases (36%)

Table 2 Pathologic parameters and outcome

Pathologic parameter	
Tumor size	0.6 cm- 8.2 cm
% Invasion	0–100%, average 46%
Tumors with solid growth	$N = 5$; range 18–50%
Tumors with solid growth (cribriform pattern)	$N = 12$; range 5–80%
Tumors with papillary growth	N = 5; range 5–80%
Tumors with acinar growth	$N = 19$; range 10–100%
Tumors with colloid areas	$N = 9$; range 20–100% (2–100%)
STAS, all types, n	22 (73%)
STAS, single cells, solid nests, clusters, n	14 (47%)
STAS, micropapillary type, n	8 (27%)
STAS, grade 1: STAS, grade 2 n	11:11
Outcome	N (%)
Distant metastasis	7 (23%)
Lymph node metastasis	3 (10%)
Lung spread beyond lobe	7 (23%)
Deceased	11 (37%)
Dead of disease	5 (17%)

showed entirely invasive architecture without a lepidic component.

In 16 cases the predominant mucin-producing cell was cuboidal type; in 14 cases, columnar cells predominated. There was no significant correlation between mucin type and growth pattern or presence of STAS. Cribriform and signet ring cell patterns correlated with colloid areas ($p = 0.002$ and $p = 0.003$, respectively).

STAS of any type was present in 22 (73%) of cases. Of these, 14 (47% of all tumors) showed STAS limited to within 0,5 mm of the border of the tumor (27% of all tumors, grade 1) and the remainder showed STAS present beyond this distance (> 0.5 mm) (Fig. 4).

Some degree of TTF-1 positivity was present in 13 cases overall (43%) ($n = 11$ for cuboidal predominant tumors; $n = 2$ for columnar predominant tumors). For columnar cell predominant cases 2/14 (14%) cases showed focal TTF 1 reactivity; in none of these tumors was TTF1 diffusely positive. A higher proportion (11/16 or 69%) of cuboidal predominant tumors showed some TTF1 positivity; of these, 9 cases (82%) showed diffuse staining and 2 (18%) showed focal reactivity ($p < 0.01$).

There was a positive correlation between the proportion of micropapillary features and STAS ($P = .05$) and the degree of cribriform growth and STAS ($p = 0.03$). There was no correlation between STAS and other histopathologic parameters.

There was no significant association between any pathologic variable and death outcome. Local recurrence developed in 7 patients, determined by open surgical biopsy in 6, and imaging in 1. There was a significant association between STAS and lung recurrence (Fig. 4). There was no association between local recurrence and other pathologic parameters ($p > 0.1$). Distant metastasi bns developed in 7 patients (4 brain, 1 soft tissue, 1 adrenal, one vertebra and liver). Metastasis was determined by imaging in 5 patients, biopsy in 1 patient, and cerebrospinal fluid cytology in one patient. There was a significant association between distant metastasis and solid invasive growth (Fig. 5). There was no association between other pathologic parameters and distant metastasis ($p > 0.1$).

Discussion

The current study demonstrates that STAS is a frequent finding in mucinous adenocarcinomas of the lung, rendering the newly created categories of "mucinous adenocarcinoma in situ" and "minimally invasive adenocarcinoma" very rare. (Travis et al. 2015) In fact, these entities were not represented in the current study despite several cases showing entirely lepidic architecture, either because of size criterion (> 3 cm) or presence of STAS.

Mucinous adenocarcinomas of the lung have been subclassified and defined in various ways. The WHO classification currently views invasive mucinous adenocarcinoma as a "variant" and therefore not subject to pattern subclassification. It is defined by the presence of "abundant" intracytoplasmic mucin and has a predilection for multicentricity, large areas of in-situ growth, and by KRAS(-Kirsten rat sarcoma viral oncogene) mutations. (Travis et al. 2015) It has been appreciated that "mucinous adenocarcinomas" can show predominantly extracellular mucin, as opposed to both intra- and extracellular mucin, and that these so-called "mucus out of cell" tumors are less likely to harbor KRAS mutations. (Cai et al. 2014) A recent study including both small biopsies and surgical resections has found that ALK fusion protein is more frequently seen in invasive mucinous adenocarcinomas

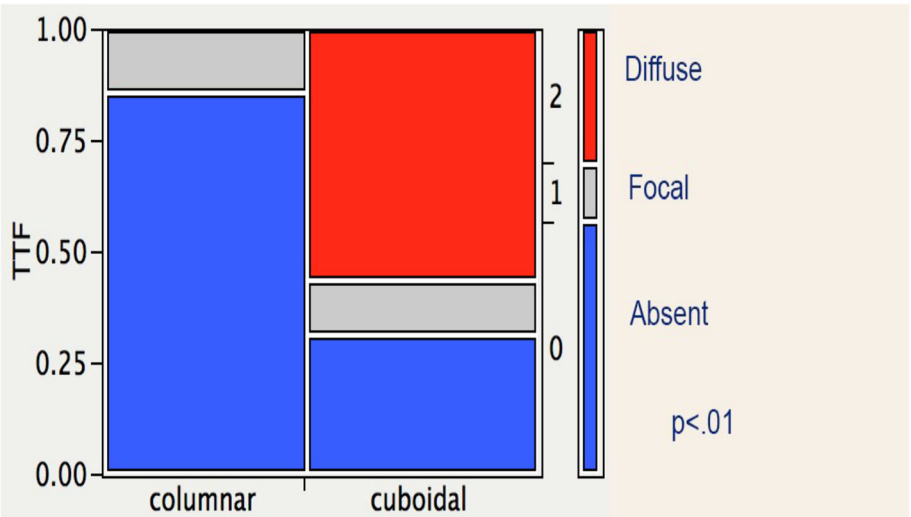

Fig. 4 TTF-1 immunoreactivity, extent compared to mucin cell type

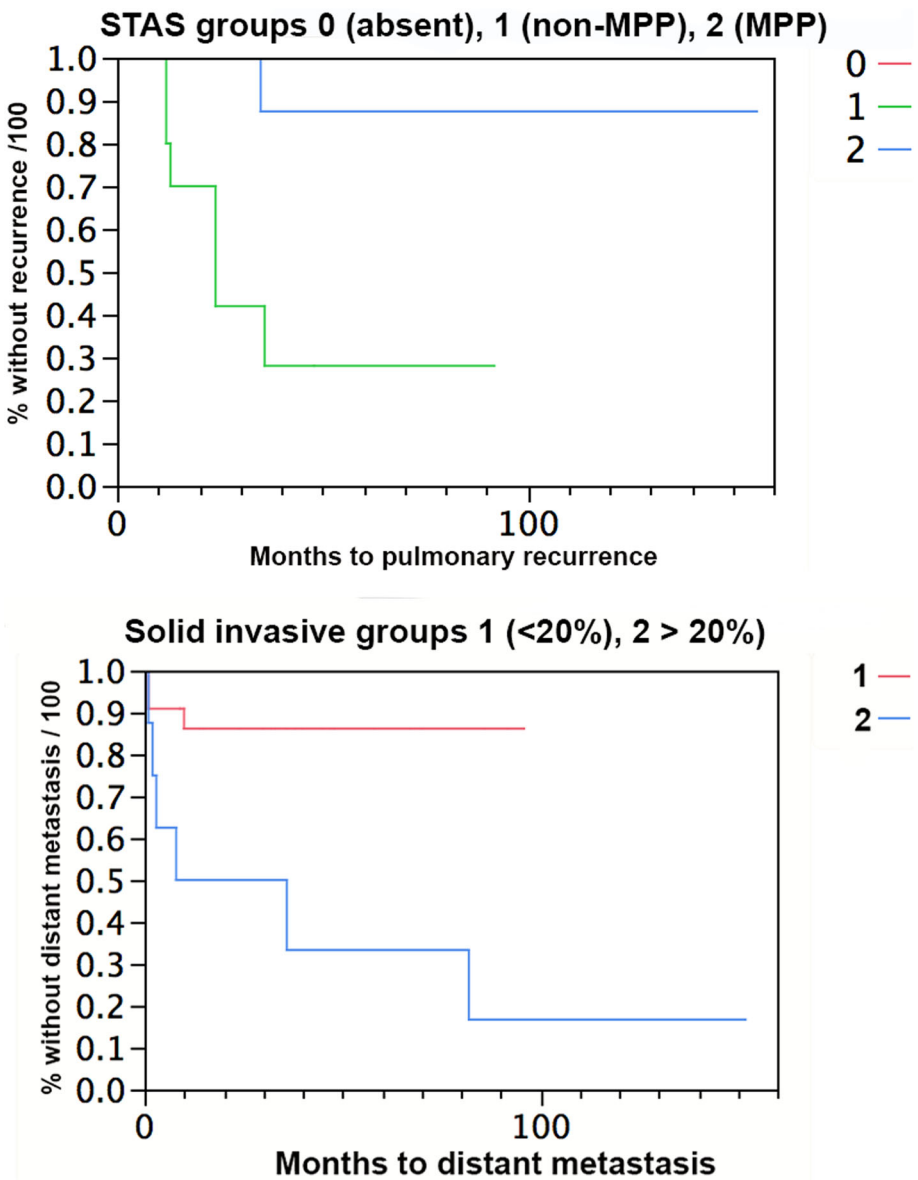

Fig. 5 Time-adjusted Kaplan Meier curves relating STAS to local recurrence (top) and proportion of solid growth to distant recurrence (bottom). There was a significant increase in the rate of local recurrence by STAS ($p = .005$) and in the rate of distant recurrence by solid invasive group ($p = .003$)

than in other adenocarcinomas. (Zhao et al. 2016) Although it is well known that the tumor cells may resemble either goblet cells or cuboidal cells, in the current study the latter showed some intra-cytoplasmic mucin, at the very least along the brush border; these cuboidal cells were more likely to express TTF-1. Another variant of adenocarcinoma is "colloid" carcinoma, which is associated with a high rate of STAS and not infrequent expression of enteric antigens such as CDX-2. (Rossi et al. 2004) Although historically the term "colloid" has been used interchangeably with "mucinous", the most recent WHO classification considers colloid carcinomas as a separate variant of adenocarcinoma, specifically defined by inconspicuous lepidic growth and airspaces distended with mucus containing tumor nests. (Rossi et al. 2004) Our study found a great deal of morphologic overlap between invasive mucinous adenocarcinomas and colloid carcinomas, therefore we included two cases of pure colloid carcinoma in this study. Several recent studies of mucinous tumors have noted the difficulty in distinction between colloid and invasive mucinous adenocarcinomas, and because of this, mucinous tumors have been generally grouped together. (Geles et al. 2015; Masai et al. 2016) A mucinous variant of micropapillary carcinoma has also

been described, which corresponds to mucinous carcinomas in the current study with micropapillary STAS. These tumors have been associated with ALK-1 (anaplastic lymphoma kinase-1) gene rearrangements and her2 mutations. (Kamata et al. 2016)

The pathologic features of mucinous adenocarcinomas that are associated with poor prognosis have not been studied in detail. Qu et al. demonstrated that large size and presence of invasion were associated with a bad outcome. (Qu et al. 2015) Jessurun et al. published two patients with non-invasive colloid carcinoma and a prolonged disease free survival. (Jessurun 2015) The presence of signet ring type of invasive lesion is a poor prognostic sign in the colloid variant of pulmonary mucinous adenocarcinoma. (Rossi et al. 2004) Geles et al. published one of the most comprehensive studies on mucinous tumors of the lung and found only TNM stage and loss of P16 expression to impact survival. (Geles et al. 2015) In this latter study, more than half of the mucinous tumors had mutations in the KRAS gene and even tumors with CK20 positivity, most of them expressed TTF-1, a finding that is similar to the one in the current study.

Previous published reports have shown STAS to be an indicator of poor prognosis. Kadota et al. showed that in a subset of patients with peripheral, predominantly non-mucinous adenocarcinomas < 2 cm, STAS was highly associated with regional recurrence, especially in tumors that were treated with sub-lobar resections. (Kadota et al. 2015) Onozato et al. showed a significantly increased 5-year recurrence-free survival for patients without STAS ("tumor islands"), in a series also of predominantly non-mucinous tumors. (Onozato et al. 2013) Onozato et al. focused on "large" islands that were at least "several alveoli" separated from the edge of the tumor.

The definition of STATS, while accepted in the current WHO Classification, is not consensual. An autopsy study by Thunissen et al. describe the spreading of tissue fragments and individual cells through a knife surface as one of the possible artifacts in lung specimens. {Thunnissen, 2016 #43} An older study on breast tissue describes tissue displacement in breast tissue and in a high percentage of cases. {Diaz, 1999 #45}.

spreading of tissue fragments and individual cells through a knife surface.

Our study is the first to look at STAS as a prognostic parameter in mucinous adenocarcinomas only. Similar to published reports, we found STAS to be associated with poorer prognosis, but only in the sense of local recurrence. We found no correlation with distant recurrence. Solid growth in the tumor was significantly associated with distant metastases, suggesting that architectural patterns- particularly micropapillary patterns and solid growth- that are known to portend poorer prognoses in non-mucinous adenocarcinomas (Warth et al. 2012) are important parameters in the mucinous subset as well. In keeping with findings by Strand et al. who studied a series of mucinous and nonmucinous lepidic predominant tumors, the percentage of the invasive component was significant, and showed an inverse correlation with time to distant metastasis. (Strand et al. 2015)

Given these findings, we suggest that mucinous adenocarcinomas be subclassified and graded in the same manner as their non-mucinous counterparts: with specific note to percentage of solid growth, micropapillary architecture, STAS, and size of invasive component. Histologic subclassification in a manner identical to nonmucinous tumors may provide valuable prognostic information.

Conclusions

Mucinous adenocarcinomas of the lung are similar to non-mucinous and both STATs and solid growth represent poor prognosticators, for local and distant recurrence, respectively. The growth patterns of mucinous adenocarcinomas should be reported like reporting of non-mucinous adenocarcinomas.

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

AP and AB reviewed all the slides and performed morphological evaluation of histology. FT and AB participated in the design of the study and performed the statistical analysis. AB, FT an AP conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Consent for publication

not applicable.

Competing interests

The authors declare that they have no competing interests. No external funding was used.

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