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Comparative Characteristics of Napsin A, TTF 1 and EGFR Mutation Expression in Mucinous Lung Cell Carcinomas

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Background: Invasive mucinous lung adenocarcinomas are rare and account for 2%–10% of all lung adenocarcinoma cases. It is believed that Napsin A exhibits a weaker expression in mucinous adenocarcinomas compared with TTF1, but such correlation is still poorly researched.

Aim: The aim of the study was to determine the frequency of mucinous to non-mucinous adenocarcinomas and compare specificity and sensitivity of monoclonal Napsin A with TTF1 in mucinous adenocarcinomas and define the frequency of EGFR mutations.

Materials and methods: Eighty-four resected lung carcinomas were prospectively evaluated. All biopsies were analysed with p63, TTF1, monoclonal Napsin A, CK7, CK20 and CDX2 and were studied with real-time PCR technology.

Results: In resected material we detected 49/84 (58.3%) adenocarcinomas and selected 21 mucinous adenocarcinomas out of 46 non-mucinous adenocarcinomas (45.6%). The most common pattern of mucinous adenocarcinomas is papillary - 24% and colloidal - 24%, followed by acinar - 19.2% and lepidic - 19.2%. mNapsin A was positive in 18/21 (85.7%) mucinous adenocarcinomas v/s 17/21 TTF1 positive (80.9%). EGFR mutations were detected in 3/21 cases with mucinous adenocarcinomas (14.3%): mucinous papillary, mucinous acinar and "salivary gland-like".

Conclusion: Our study demonstrates a high proportion of primary mucinous lung adenocarcinomas to primary non-mucinous adenocarcinomas. Sensitivity and specificity of mNapsin A and TTF1 did not show significant difference in pulmonary mucinous and non-mucinous adenocarcinomas, as mNapsin A gave greater sensitivity to mucinous adenocarcinomas. Our results indicate the same mutation frequency of EGFR in mucinous adenocarcinomas as mutation frequency detected in non-mucinous adenocarcinomas in the Bulgarian region.

BACKGROUND

A new classification of adenocarcinoma (AC) of the lungs was published in 2001. One of the major changes is the reclassification of the carcinoma formerly known as mucinous bronchioloalveolar carcinoma (BAC) to "invasive mucinous adenocarcinoma (IMA)". IMA was classified in a new category due to its unique radiologic, morphologic and genetic characteristics.^{1,2}

An important morphological feature of mucinous adenocarcinomas (MAC) of the lung is mucin in the alveolar spaces and in tumor cells. These tumors histologically may also indicate alveolar, acinar, papillary, micropapillary or solid differentiation as

non-mucinous AC. They should be distinguished from metastatic mucinous carcinomas of the colon, breast, stomach and others.^{2,3}

Immunohistochemical (IHH) expression of *Napsin A* in primary pulmonary mucinous carcinomas is not well studied. It turns out that contrary to perceptions, primary lung adenocarcinomas with extracellular and intracellular mucin production are not uncommon. It is believed that *Napsin A* (*NapsA*) exhibits a weaker expression in MAC compared with *TTF1*, but such correlations are still poorly researched.⁴

It is also considered that the histological subtype of adenocarcinomas, which is not an association with *EGFR* mutations, is the type with mucinous

differentiation. *EGFR* mutations were not found in invasive mucinous adenocarcinomas or mucinous bronchioloalveolar adenocarcinomas (lepidic adenocarcinomas).⁴ Typically, these tumors are associated with mutations in *KRAS*.⁵ There are reports of greater chemoresistance in tumors previously categorized as BAC.^{6,7}

The aim of our study is to determine the frequency of mucinous to non-mucinous AC, to comparable specificity and sensitivity of *Napsin A* with *TTF1* in MAC and determine the frequency of *EGFR* mutations.

MATERIALS AND METHODS

BIOPSY SELECTION

From January 2013 to February 2015, we selected patients with newly diagnosed primary lung cancer which were consecutively enrolled. Inclusion criteria for this study were: 1) patients undergone complete resection of the primary lesion; 2) patients with clinically confirmed primary tumor in the lung; 3) samples had a minimum of 200 tumor cells per block and sufficient corresponding normal tissue for mutational analysis.

Eighty four resected lung tumors were evaluated according to the new IASLC/ATS/ERS lung adenocarcinoma classification for resected material. Invasive mucinous adenocarcinomas were defined as a tumor with lepidic, acinar, papillary or micropapillary pattern, salivary gland-like tumor or colloidal AC with abundant extracellular mucin. Colloid-predominant adenocarcinoma was defined as a tumor with mucin pools within airspaces, with destruction of alveolar walls. Extracellular mucin was considered to be positive when observed in $\geq 50\%$ of the tumor. All samples were tested with monoclonal antibody *Napsin A* (*m-Napsin A* antibody) and *TTF1*.

IMMUNOHISTOCHEMICAL ANALYSIS

The 4- μ m unstained slides were used for detection of the following antigens: NCL-L-*Napsin A* (monoclonal mouse; IP64, Novocastra, 1:400); *TTF-1* (monoclonal mouse; SPT24, Dako, 1:200), CK7 (monoclonal mouse; OV-TL 12/30, Dako Cytomation), CK20 (monoclonal mouse; Dako Cytomation), CDX2 (monoclonal mouse; BioGenex). For antigen retrieval, formalin-fixed, paraffin-embedded tissue sections were deparaffinized, hydrated, and heated in a steamer at an appropriate pH. Subsequently, slides were washed in Tris-buffer. Endogenous peroxidase was blocked with 3% H_2O_2 for 5 minutes. Primary

antibody incubation was performed for 1 hour at room temperature. Secondary antibody incubation with Post Primary Block was done for 25 min., followed by DAB Chromogen 1.74% (3,3'-diaminobenzidine tetrahydrochloride, Novo Link Polymer Detection System) application for 5 minutes. Chromogenic signal and compartmentalization were assessed by bright-field microscopy and graded.

EGFR MUTATION ANALYSIS

All the specimens were formalin-fixed paraffin-embedded (FFPE) tissue blocks obtained during surgical excision of the tumors. It had used 10 sections (5 μ m thick) of paraffin block to isolate DNA. The FFPE tissue DNA extraction came from QIAamp DNA FFPE Tissue Kit of Qiagen (Hilden, Germany). Exons 18-21 of *EGFR* were analysed by using polymerase chain reaction (PCR) based on Scorpions Amplification Refractory Mutation System (SARMS) technology. The specifically designed *EGFR*RRGQ PCR Kit allows the detection of 29 known somatic mutations (including the inhibitory mutation T790M) in exons 18-21 of the *EGFR* genes.

STATISTICAL ANALYSIS

We adopted Pearson's χ^2 test or Fisher's exact test to assess the correlations between pathological variables of IHH stains (*TTF1* and *Napsin A*). The statistical analyses were performed using SPSS 17.0 for Windows.

RESULTS

HISTOLOGIC FEATURES

Of 84 resected lung cancers, we found 49/84 ACs (58.3%). Three tumors were negative to all pulmonary markers and expressed CDX2 and CK20 and were evaluated as metastases of mucinous colorectal carcinomas (CRC) and were excluded from evaluation. We expected 46 primary lung AC. Mucinous ACs were 21/46 (45.6%) and 25/46 (54.3%) were non-mucinous ACs. The most common pattern of mucinous carcinomas was papillary and colloidal, followed by acinar and lepidic. *Napsin A* was positive in 18/21 (85.7%) MAC v/s 17/21 *TTF1* positive (80.9%). CK7 was positive in 18/21 MAC (85.7%), (**Fig. 1**). CDX2/CK20 was negative in all expected cases of primary mucinous lung carcinomas (**Table 1**). Most common pattern of non-mucinous carcinomas was solid - 48.0%, followed by papillary and micropapillary AC - 46.0%.

Figure 1A. Colloid lung adenocarcinoma. H.E. Original magn. x40.

Figure 1D. Mucinous papillary adenocarcinoma. H.E. Original magn. x40.

Figure 1B. Napsin A, intensive cytoplasmic expression. Original magn. x200.

Figure 1E. Napsin A, Original magn. x200.

Figure 1C. TTF1, intensive nuclear expression. Original magn. x200.

Figure 1F. TTF1, Original magn. x200.

Table 1. Immunohistochemical analyses in mucinous and non-mucinous adenocarcinomas

Type	Nº	%	Napsin A	TTF1	CK7	CDX2/CK20
Adenocarcinomas:	46/84	54.8	+	+	+	
Mucinous:						
Papillary	5/21	24.0	4/5	4/5	5/5	–
Colloid	5/21	24.0	5/5	5/5	5/5	–
Acinar	4/21	19.2	3/4	2/4	4/5	–
Lepidic	4/21	19.2	4/4	4/4	4/5	–
Signet ring	2/21	9.6	0/2	0/2		–
Salivary gland-like tumor	1/21	4.8	2/2	2/2		–
Total	21/46	45.6				
Non-mucinous:						
Solid	12/25	48.0	8/12	11/12	12/12	
Papillary and micropapillary	6/25	46.0	5/6	5/6	6/6	
Acinar	5/25	20.0	5/5	4/5	4/5	
Lepidic (BAC)	1/25	4.0	1/1	1/1	0/1	
Clear-cell	1/25	4.0	0/1	0/1	1/1	
Total	25/46	54.3				

EGFR MUTATIONS

EGFR mutations were detected in 3/21 cases with mucinous AC (14.3%): mucinous papillary, mucinous acinar and salivary gland-like AC (**Fig. 2**). Among non-mucinous AC, mutation frequency is 4/25 (16%) in this selected group (**Table 2**).

DISCUSSION

Invasive MAC account for 2%–10% of lung adenocarcinoma cases in East Asia, Europe, and the United States.^{8,9} They are considered to be more malignant than other common subtypes of lung adenocarcinoma such as lepidic and acinar subtypes.¹⁰ MAC in the lung is a rare, but distinctive variant of pulmonary adenocarcinoma. In one of the largest series described by Rossi G et al. (2004)² MAC accounted for 0.24% of all lung cancers and the prognosis was often favorable. However, some recent reports have described a rare and aggressive clinical feature.¹¹ According to the latest WHO classification of lung and pleural tumors, a diagnosis of MAC should be limited to findings of neoplastic cells floating in large pools of mucus and focally lining the alveolar spaces.³

Morphological response of mucin-producing carcinomas of the lung is extremely wide and is represented by several histologic subtypes including mucinous bronchioloalveolar adenocarcinoma, colloidal adenocarcinoma, annular-cell adenocarcinoma and mucinous cistadenocarcinoma.¹² Their diagnosis and differentiation from other subtypes of lung carcinomas are easy to make because of the formation of glandular structures and the production of mucus. Difficulties arise from possibilities of differentiated metastatic gastrointestinal and mucinous ovarian adenocarcinomas.

Mucinous adenocarcinomas of the lung show a strong tendency toward multicentre growth pattern, multilobular and bilateral pulmonary airy distribution. Therefore, mucinous components must be described. MAC, which account for 2%–10% of lung adenocarcinoma cases in East Asia, Europe, and the United States, were considered to be more malignant than other common subtypes of lung adenocarcinoma, such as lepidic and acinar subtypes.⁸

It turns out that contrary to perceptions, primary lung adenocarcinomas with extracellular and intracellular mucin production are not uncommon. On

Figure 2A. Salivary-gland-like lung adenocarcinoma with mutation in EGFR – deletion in exon 19. Adenoid-cystic appearance, H.E. Original magn. x40

the basis of morphological performance Cai D et al. (2014)¹³ divided lung MAC into two subgroups: mucus-in-cell adenocarcinoma (MICA) and mucus-out-of-cell adenocarcinoma (MOCA). They found that patients with MICA showed a potential trend of better prognosis than the mucus-negative patients, while MOCAs seemed to have the worst prognosis of all three subgroups. When the mucus is out of the cell, the tumor may have aggressive biological behavior. These results indicated that IMA subtype alone may not be an adequate predictor for worse prognosis.¹³

In our study, the proportion of primary mucinous AC also was high 21/46 – 45.6%. *NapsA* was negative in 4 MAC (19.2%). Currently, thyroid transcription factor 1 (*TTF1*), which is a nuclear

Figure 2B. Salivary-gland-like lung adenocarcinoma with mutation in EGFR – deletion in exon 19. TTF1, Original magn. x200.

Figure 2C. Salivary-gland-like lung adenocarcinoma with mutation in EGFR – deletion in exon 19. CK7, Original magn. x200.

expression protein in type II pneumocytes and Clara cells of the lung, is the most commonly used immunohistochemical marker for identification of lung AC. It is believed, however, that *TTF1* is less

Table 2. EGFR mutations in mucinous adenocarcinomas:

MAC subtype	Sex	Year	Smoking history	EGFR Mutation	Therapy with TKI	
					Time	Progression
Mucinous papillary	m	55	Active 30PY	20 Ins	no	†
Mucinous acinar	f	75	no	L858R	4 mos	progression
Salivary gland-like AC	m	61	Former 30PY	19 Del	no	†

Legend: Del: deletion; Ins: insertion; PY: pack years; †: lethal outcome; mos: months

specific in distinguishing primary and metastatic adenocarcinomas of the lung, because in certain types of mucin-producing lung tumors, especially mucinous BAC, *TTF1* expression often is absent.¹⁴ In our study, *TTF1* was negative in 5/21 mucinous AC (24.0%). This confirms the high percentage of *TTF1*-negative mucinous adenocarcinomas in the lung. On RM, *TTF1* in mucinous AC is a less sensitive marker of *Napsin A* in terms of false negative samples (80.9% v/s 85.7%, $\chi^2 = 0.102$).

Rekhtman N (2015)¹⁵ found that polyclonal NapsA had at least focal labeling in nearly all (24 of 25) tested tumors, regardless of the site of origin. In contrast, m-NapsA antibody was completely negative in all extrapulmonary carcinomas. We do not find significant differences in sensitivity of the m-NapsA antibody and *TTF1* to pulmonary MAC; 4 v/s 5 negative biopsies. In 17/21 MAC both markers were positive (81.6%), as a diffuse strong expression (N3) was observed in 20/21 tumors tested with *TTF1* (96.0%), v/s 11/21 with intense cytoplasmic expression of *NapsA* (52.8%). This indicates a weaker intensity on expression of NapsA in mucinous AC, but not at a lower specificity compared to *TTF1*. Monoclonal antibody *NapsA* was completely negative in all metastatic mucinous adenocarcinomas.

Wu J et al. (2013)¹² studied 43 primary mucinous lung AC and 25 mucinous metastatic AC. They observed that overall sensitivity of *NapsA* (33%) in mucin-producing adenocarcinomas of the lung is lower than *TTF-1* (42%) sensitivity. Compared with *NapsA*, *TTF-1* expression is found more frequently among the majority of solid adenocarcinomas with production of mucin, colloid adenocarcinomas and signet ring cell adenocarcinomas. In tumors, previously classified as mucinous bronchioloalveolar carcinomas, positivity of *TTF-1* was identical to that of *NapsA* (11%).

In some recent immunohistochemical studies, however, it has been reported that *NapsA* expression in squamous cell carcinoma of the lung can reach 26%, which raises doubts that this marker might not be specific to lung adenocarcinomas, as is commonly believed. In a study of Ordóñez NG et al. (2012)¹⁶ and also in our materials, it was found that because of the strong reactivity of *NapsA* in hyperplastic type II pneumocytes and alveolar macrophages, both of which are included within the tumor, incorrect diagnosis of mixed histologic subtype may sometimes be made. We also decided that the presence of these interpolated cells is the most likely cause of discrepancies. mNapsA displays strong expression in tissue macrophages and hyperplastic pneumocytes type II, which is a disadvantage in small materials, and can cause potential errors. Pathologists should be aware of this potential pitfall in interpretation of immunostaining for *NapsA*, especially in small samples and endoscope biopsies, lung tissue microarrays or cor biopsies.

In our study, of greater significance is the coincidence of negative results. Double negative of mNapsA/*TTF1* were 6/46 MAC (13.2%). In this study, both markers did not show significant difference between sensitivity and specificity of mNapsA – 37/46 (81.4%) v/s *TTF1* positive – 38/46 (83.6%); (CI: 0.98-1.33; $\chi^2 < 0.001$) in both mucinous and non-mucinous AC. Three metastases from colon, mucinous AC, were double negative which allowed for additional typing with CK20 and CDX2 their differentiation from primary lung MAC. Double negative turned out to be an atypical carcinoid with mucinous acinar structures (Synaptophysin+). A primary outbreak in the small intestine was found in abdominal ultrasound scan.

Zenali MJ et al. (2015)¹⁷ indicated frequent CDX2 expression in *colloid carcinomas*. Immu-

nohistochemical studies showed CK7, CK20, and CDX2 expression in all tumors, whereas *TTF-1*, surfactant A, and *NapsA* were not present or were only focally positive in most cases. Colloid lung carcinomas have showed overlapping results in immunoprofile with enteric-type adenocarcinoma: CK7 100%; CK20 85%; *TTF-1* 28% and *NapsA* – 0 cases, in contrast to the results reported by Rossi G et al.²: CK7 81.8%; CK 20 54.5%; *TTF1* 61%. EGFR mutations are absent in this study. On the contrary, we detected a 100% diffuse or focal expression of CK7; *TTF1* and *NapsA* was expressed in all 5 colloidal AC. Every tumor was CDX2/CK20 negative. Three metastases of mucinous colorectal carcinomas were CDX2/CK20 variable positive and CK7; *TTF1* and *NapsA* completely negative.

Invasive mucinous adenocarcinomas were associated with KRAS transition mutations. AC with extracellular mucin was associated with KRAS mutations, whereas signet-ring cell feature was not associated with EGFR or KRAS mutations. Among invasive mucinous adenocarcinomas with KRAS mutations, a pure mucinous pattern was more common than a mixed mucinous/non-mucinous pattern.¹⁸

EGFR mutation was rarely found in solid predominant and mucinous AC. Chen Zh et al. (2014) found that the presence of well-differentiated components in lung adenocarcinoma, such as lepidic, papillary and acinar, indicates a higher EGFR mutation rate, while the solid and mucinous component indicates a lower EGFR mutation rate.¹⁹ Based on 382 examined lung adenocarcinomas Sun PL (2012) obtained similar results as ours for the expression of EGFR - 13.3% in IMA (mucinous BAC). EGFR mutations were significantly more common in tumors with thyroid transcription factor-1 (*TTF-1*) expression than those without *TTF-1*, and almost all (92.7%) mutated adenocarcinomas were *TTF-1* positive. *TTF-1* can predict EGFR mutations. In this study, mixed (Acinar and BAC) and (Papillary and Acinar) patterns of lung adenocarcinomas with EGFR/*TTF-1* protein expression are more frequently associated with EGFR mutations.²⁰ Zang Y et al. (2015) studied 1042 lung adenocarcinoma patients. The results demonstrated that a lack of *TTF1* expression was identified more frequently in male smokers with large tumors that present advanced disease stage. *TTF1* - correlated with solid and invasive mucinous subtypes of lung adenocarcinoma and lower frequency of EGFR mutations. It defines a subgroup of lung adenocarcinomas with unfavorable outcomes.²¹

Solid patterns showed lower *TTF1* and higher Ki-67 expression. *TTF1* expression was higher in non-mucinous lepidic and micropapillary patterns when compared to acinar and solid and acinar, solid and mucinous respectively. Mucinous subtypes and solid patterns show lower expression of nuclear *TTF1* and higher expression of Ki67, reflecting probably a particular cell origin and more aggressive biological behaviour and have to be reported as lung adenocarcinomas, avoiding poorly differentiated carcinoma designation.²²

Our results did not indicate significant differences between sensitivity and specificity of *TTF1*/*NapsinA* in both mucinous and non-mucinous adenocarcinomas in the lung and the same mutation frequency of EGFR in mucinous AC - 3/21 cases (14.3%) as mutation frequency detected in non-mucinous AC in Bulgarian region – 10-15%.

CONCLUSION

We found a high proportion of primary mucinous lung AC to primary non-mucinous AC. Sensitivity and specificity of *mNapsA* and *TTF1* did not differ significantly in pulmonary mucinous and non-mucinous AC in the RM, as *mNapsA* gave greater sensitivity to mucinous AC.

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Сравнительные характеристики Napsin A, TTF 1 и EGFR экспрессии мутаций при муцинпродуцирующих карциномах клеток лёгких

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Введение: Инвазивные муцинопродуцирующие аденокарциномы лёгких являются сравнительно редкими и представляют собой 2%-10% всех случаев аденокарцином лёгких. Предполагается, что Napsin A проявляет более слабую экспрессию по сравнению с TTF1, но подобная взаимосвязь всё ещё недостаточно исследована.

Цель: Целью настоящего исследования является определение частоты проявления муцинпродуцирующих по сравнению с немучинопродуцирующими аденокарциномами и сопоставление специфичности и чувствительности моноклонального Napsin A с TTF1 при муцинпродуцирующих аденокарциномах и определение частоты EGFR мутаций.

Материалы и методы: Была проведена проспективная оценка резецированных карцином лёгких в количестве восьмидесяти четырёх. Все биопсии были анализированы с применением p63, TTF1, моноклонального Napsin A, CK7, CK20 и CDX2 и были исследованы с применением ПЦР (полимеразная цепная реакция) технологии в реальном времени.

Результаты: В резецированном материале было установлено 49/84 (58.3%) аденокарцином и выделено 21 муцинпродуцирующая аденокарцинома из 46 немучинопродуцирующих аденокарцином (45.6%). Наиболее часто встречающейся моделью муцинопродуцирующей аденокарциномы является папиллярная - 24% и коллоидная - 24%, а далее ацинозная - 19.2% и лепидичная - 19.2%. mNapsin A являлся положительным при 18/21 (85.7%) муцинпродуцирующих аденокарциномах по сравнению с 17/21 TTF1 положительными (80.9%). EGFR мутации были установлены в 3/21 случаях муцинпродуцирующих аденокарцином (14.3%): муцинпродуцирующие папиллярные, муцинпродуцирующие ацинозные и „подобные слюнным железам“.

Заключение: Наше исследование устанавливает большее количество муцинпродуцирующих аденокарцином по сравнению с немучинопродуцирующими аденокарциномами. Чувствительность и специфичность mNapsin A и TTF1 не показали значительных различий при лёгочных муцинпродуцирующих и немучинопродуцирующих аденокарциномах. Результаты нашего исследования устанавливают одинаковую мутационную частоту EGFR при муцинпродуцирующих с мутационной частотой, установленной при немучинопродуцирующих аденокарциномах в регионе Болгарии.