CLINICAL AND MORPHOLOGICAL FEATURES OF NON-SMALL CELL LUNG CANCER IN PATIENTS WITH DIFFERENT TYPES OF HISTOLOGICAL CHANGES TO THE BRONCHIAL EPITHELIUM

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Lung cancer occupies the leading position in the global structure of oncological diseases. Despite significant advances in its treatment, the survival remains low. Morphological changes to the bronchial epithelium outside the tumor may provide important cues on progression of the disease in patients with lung cancer. This study aimed to identify associations between morphological and clinical features of non-small cell lung cancer and morphological changes to the epithelium in small bronchi outside the tumor. The study encompassed tumor specimens collected from 90 patients, 75 (83%) men and 15 (17%) women, diagnosed with non-small cell lung cancer. The average age of the patients was 67.8 ± 7.4 years. The results indicate higher frequency of lymphogenous metastasis in patients with combined basal cell hyperplasia and squamous metaplasia (BCH+SM+ group) compared to patients with isolated basal cell hyperplasia (BCH+SM– group, $p = 0.05$). The BCH+SM– group presented with higher rates of hematogenous metastasis compared to BCH+SM+ and BCH–SM– groups ($p = 0.004$ and $p = 0.0019$, respectively), as well as increased representation of low-differentiated structures in the primary tumors. The results suggest a commonality of parenchymal-stromal interactions in non-small cell lung cancers and their surroundings and a significant impact of these interactions on differentiation status and progression of the tumors.

Keywords: non-small cell lung cancer, tumor heterogeneity, basal cell hyperplasia, squamous cell metaplasia, metastasis

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КЛИНИКО-МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО У БОЛЬНЫХ С РАЗНЫМИ ВАРИАНТАМИ ГИСТОЛОГИЧЕСКИХ ИЗМЕНЕНИЙ БРОНХИАЛЬНОГО ЭПИТЕЛИЯ

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По данным мировой статистики рак легких занимает ведущие позиии в структуре онкологических заболеваний. Несмотря на значительные достижения в лечении, выживаемость остается низкой. Изучение ассоциации морфологических изменений бронхиального эпителия смежных с опухолью у пациентов с раком легкого, может привнести значимый вклад в понимание прогрессии опухоли. Целью работы было выявить особенности морфологического строения и прогрессии немелкоклеточного рака легких, ассоциированные с характером изменений эпителия в мелких бронхах, смежных с опухолью. В исследование был включен операционный материал от 90 пациентов с диагнозом немелкоклеточный рак легкого. Средний возраст пациентов составил 67,8 ± 7,4 лет. Мужчин было 75 (83%), женщин — 15 (17%). Выявлена высокая частота развития лимфогенного метастазирования в группе пациентов с сочетанием базальноклеточной гиперплазии и плоскоклеточной метаплазии (БКГ+ПМ+) по сравнению с группой, где выявлена только базальноклеточная гиперплазия (БКГ+ПМ–) ($p = 0,05$). Частота встречаемости гематогенных метастазов была выше группе с БКГ+ПМ– по сравнению с БКГ+ПМ+ ($p = 0,004$) и БКГ–ПМ– ($p = 0,0019$). В то же время в группе высокого риска гематогенного метастазирования (БКГ+ПМ–) в первичных опухолях чаще встречаются низкодифференцированные структуры. Результаты исследования позволяют предполагать о наличии ассоциации паренхиматозно-стромальных отношений в мелких бронхах опухоленосителей и в опухоли и их связь со степенью дифференцировки НМРЛ и с его прогрессией.

Ключевые слова: немелкоклеточный рак легкого, опухолевая гетерогенность, базальноклеточная гиперплазия, плоскоклеточная метаплазия, метастазирование.

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Lung cancer occupies the first place in the structure of cancer mortality, both globally and in Russia [1].

The continued search for additional prognostic indicators in lung cancer is accompanied by extensive mechanistic studies on lung carcinogenesis. With bronchial epithelium being the main substratum and cell source of lung tumors, the condition of the bronchial epithelium outside the tumor foci in patients with lung cancer is given close consideration.

Earlier reports emphasized the relevance of research into hyperplastic processes in small bronchi located at some distance from the primary tumor. The hyperplastic lesions of the bronchial epithelium may already harbor the minute genetic changes that subsequently direct neoplastic processes and become fully actualized in carcinogenesis [2, 3].

The development of squamous cell lung carcinomas from pre-existing hyperplastic lesions in the bronchial epithelium has been largely attributed to the influence of inflammatory factors that interfere with normal cell cycle while inhibiting apoptosis and cell differentiation [4].

Basal cell hyperplasia (BCH), the first morphologically identifiable step of pathogenic alterations in the bronchial epithelium, is caused by accelerated regeneration with a simultaneous constraint on cell differentiation under chronic inflammatory conditions [5]. In BCH, the number of cell rows reaches three [6]. The cells present with no atypia, intercellular cytoplasmic bridges or keratinization while preserving the cilia at their surface [7, 8]. Nevertheless, the altered expression of proliferation and apoptosis markers (Ki67, Bcl-2, p53) is noted already in BCH [5, 9].

Squamous cell metaplasia (squamous metaplasia, SM) is defined as replacement of the columnar ciliated respiratory epithelium with mature squamous epithelium. In SM, the surface layer of the epithelium is formed by cells lying in parallel to the basement membrane, showing minimal or zero signs of atypia and connected by intercellular bridges. Maturation of the basal layer cells and preservation of the intermediate cell zone are also characteristic of SM [10].

BCH and SM frequently progress into neoplasia and/or invasive squamous cell cancer [6, 11]. Particular changes to the bronchial epithelium have been positively or negatively associated with various dysplastic and carcinogenic processes in the lung. For example, combinations of bronchial epithelial dysplasia with BCH are rare, independently of the presence or absence of SM, whereas BCH and SM are seldom found in patients with lung adenocarcinoma [2].

Apart from their role in the primary tumor pathogenesis, BCH and SM have been characterized as candidate predictors of tumor progression in non-small cell lung cancer. For example, a combination of BCH and SM without dysplasia in small bronchi correlates with higher probability of recurrence [12], whereas isolated BCH has been associated with higher risks of hematogenous metastasis [13].

Such associations can be explained by a variety of stromal immune reactions defined genetically and playing a key role in various types of epithelial-stromal interactions. The stromal immune reactions in the bronchi presumably reflect specific features of the tumor microenvironment [14].

This study aimed to identify associations between morphological and clinical features of non-small cell lung cancer and morphological changes to the epithelium in small bronchi outside the tumor.

METHODS

The study encompassed tumor specimens collected from 90 patients with non-small cell lung cancer T1-3N0-2M0 receiving treatment in the Thoracoabdominal Surgery Department at the Research Institute of Oncology of the Tomsk National Research Medical Center in 2009–2017. The inclusion criteria for the study encompassed the availability of written informed consent and the diagnosis of malignant epithelial tumor of the lung (squamous cell cancer or adenocarcinoma). The exclusion criteria encompassed refusal to participate, chronic comorbidities (tuberculosis, hepatitis C) and small-cell lung cancer. The spread of the disease was determined in accordance with the TNM staging system [15]. The pulmonary surgery amounted to lobectomy with ipsilateral mediastinal lymphadenectomy without neoadjuvant chemotherapy or intraoperative radiotherapy. The adjuvant chemotherapy was administered if indicated in accordance with the schemes: vinorelbine, cisplatin (25–30 mg/m^2 on days one and eight, 75–80 mg/m^2 i/v on day one, in 21 day cycles) or paclitaxel, carboplatin (200 mg/m^2 i/v on day one, AUC 6 i/v on day one, in 21 day cycles).

The morphological examination was conducted with an Axio Lab.A1 light microscope (Zeiss; Germany) and a Mirax Midi slide scanning system (Zeiss; Germany). The specimens were fixed in 10–12% solution of neutral formalin. Histological processing and subsequent sectioning of the formalin-fixed paraffin-embedded tissues were carried out by standard techniques. The sections were stained with hematoxylin and eosin (H&E).

Histological type of the tumor was determined based on the current WHO classification [16]. Only cases of squamous cell carcinoma or adenocarcinoma of the lung were selected for the study. The diagnoses were verified by immunohistochemical assessment using specific antibodies to TTF (clone SPT24, Novocastra; Leica Biosystems, UK), Napsin A (clone NCL-L, Novocastra; Leica Biosystems, UK), p63 (клон 7JUL, Novocastra; Leica Biosystems, UK), Cytokeratine 7 (clone OV-TL 12/30, Novocastra; Leica Biosystems, UK) and Cytokeratine 5/6 (clone D5/16, Dako; Agilent, Denmark). Immunostaining on slides was carried out by standard protocols. Adenocarcinomas stained positively for Cytokeratine 7, TTF and Napsin A and negatively for p63 and Cytokeratine 5/6. Squamous cell carcinomas stained positively for p63 and Cytokeratine 5/6 and negatively for Cytokeratine 7, TTF and Napsin A.

In adenocarcinoma, the parenchymal component was represented by lepidic, acinar, papillary, micropapillary or solid architectures, and occasionally by solitary tumor cells. Lepidic patterns were recognized by atypical cuboidal cells lining the alveoli from inside. Acinar patterns comprised rounded or oval glandular clusters of atypical cells. Papillary patterns comprised papillae with fibrovascular core and epithelial lining composed of atypical cuboidal or columnar cells. Micropapillary patterns comprised diminutive papillae without fibrovascular cores. Solid patterns comprised large sheets and nests of tumor cells.

In squamous cell carcinoma, the parenchymal component was represented by five types of structures: I) keratinized; II) composed of atypical non-keratinized spinous cells; III) composed of atypical basaloid cells; IV) composed of atypical, distinctly polymorphous cells; V) solitary tumor cells [17]. The analysis involved identification of these structures and determination of their abundance in a tumor (Fig. 1).

The analysis also accounted for the degree of tumor differentiation (high, medium or low) and condition of the stroma within the neoplasm. The degree of stromal development across the tumor, as well as in the vicinity of each particular type of parenchymal architecture within the neoplasm, was determined using a three-point scale (1 point — sparse stroma, less than 30% of the tumor bulk; 2 points — moderately

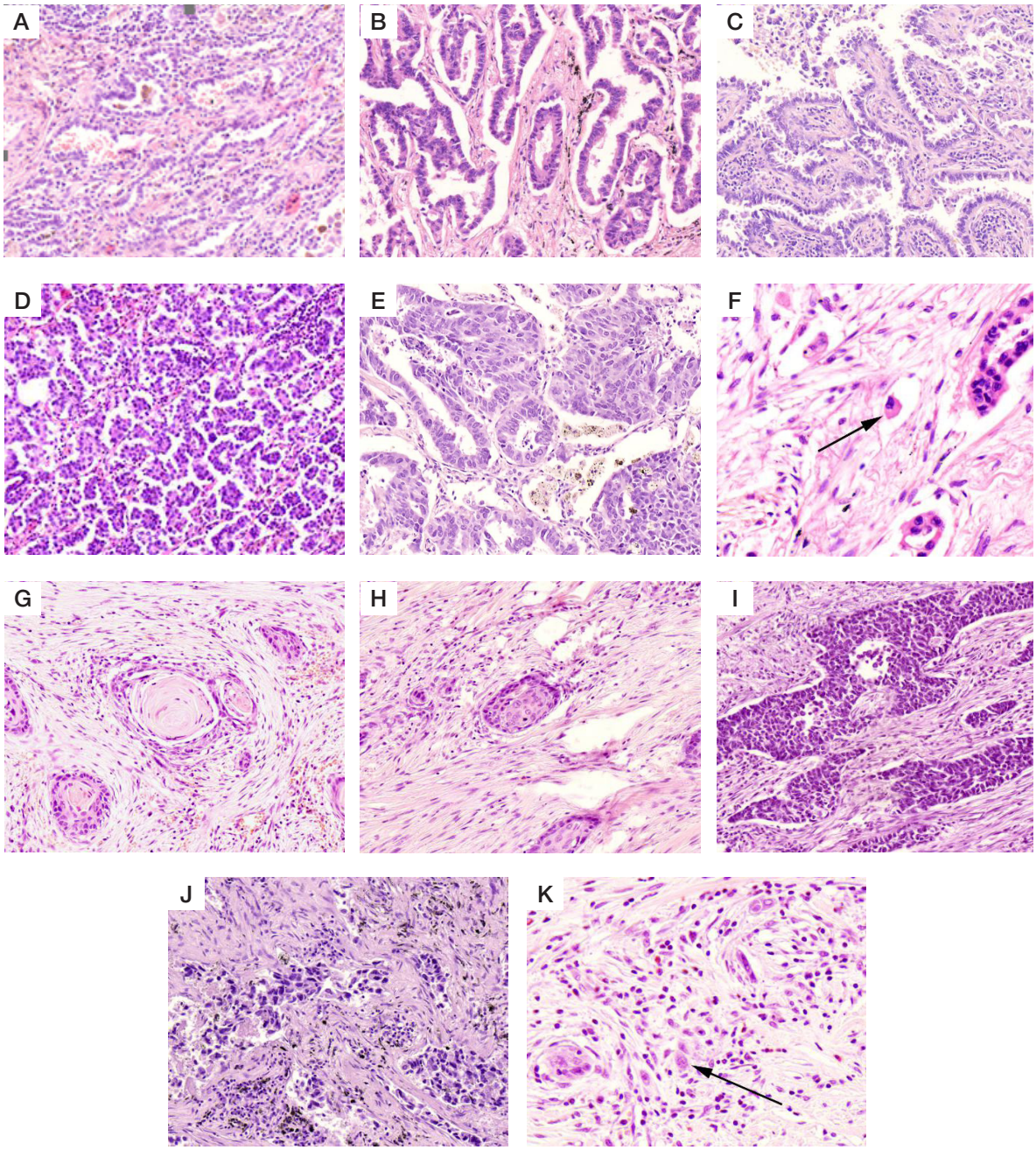

Fig. 1. Morphological subtypes of the parenchymal component of primary tumors in adenocarcinoma (**A**, lepidic; **B**, acinar; **C**, papillary; **D**, micropapillary; **E**, solid; **F**, solitary tumor cells) and squamous cell carcinoma (**G**, type I; **H**, type II; **I**, type III; **J**, type IV; **K**, type V). Staining H & E, magnification ×200

developed stroma, 30–70% of the tumor bulk; 3 points — abundant stroma, over 70% of the tumor bulk). The degree of inflammatory infiltration of the stroma across the tumor, as well as in the vicinity of each particular type of parenchymal architecture within the neoplasm, was quantified in percentages as described by Salgado et al [18]. To rule out a possible subjective bias, all examinations were carried out by two pathologists independently.

The mucosa of small bronchi located at a 3–4 cm distance from the tumor boundary was assessed for the presence of BCH and SM separately or in combination (Fig. 2).

The patients were distributed into three groups on the basis of histological changes to the bronchial epithelium: neither basal cell hyperplasia nor squamous metaplasia encountered (group a, BCH–SM–) — 17 pts; isolated basal cell hyperplasia (group b, BCH+SM–) — 45 pts; basal cell hyperplasia combined to squamous metaplasia (group c, BCH+SM+) — 28 pts. The lymph nodes were examined for the presence of metastatic lesions and the counts of lymph nodes with metastases were recorded. The follow-up period was 5 years. The medical histories and outpatient records were analyzed to retrieve information about the incidence, time-points and localization of hematogenous metastases and relapses.

Statistical processing of the data was carried out in the Statistica 10.0 program package for Windows (Dell; USA). The comparisons involved standard methods of descriptive statistics and the Mann–Whitney test for two independent samples. Correction for multiple comparisons was not applied. The differences were considered significant at $p < 0.05$.

RESULTS

The age of patients in the three groups of the study was similar. In all groups, most of the patients were men and the non-small

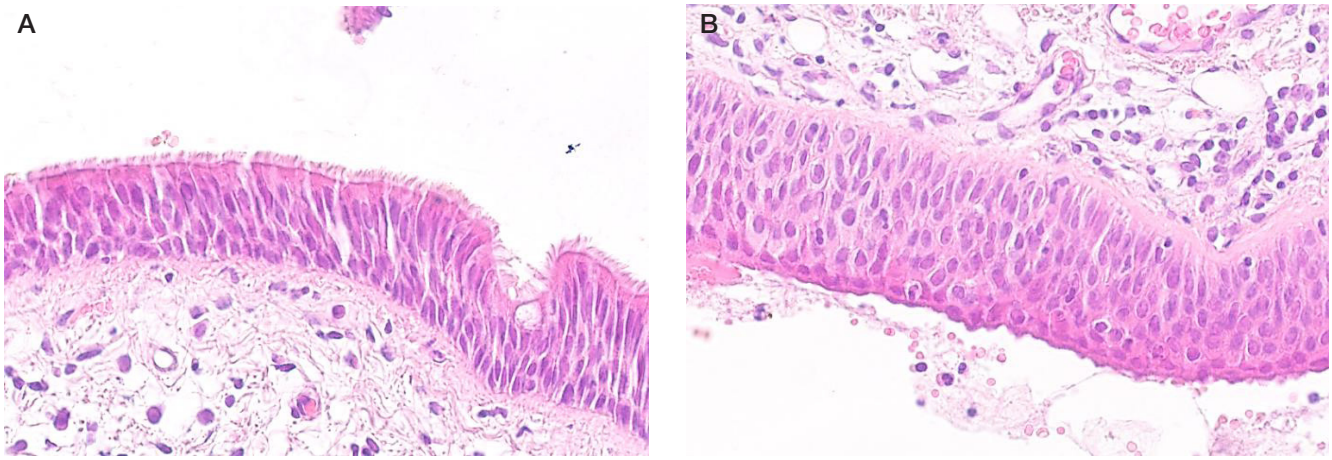

Fig. 2. Morphological changes to the bronchial epithelium outside the tumor: basal cell hyperplasia, BCH (**A**) and squamous cell metaplasia, SM (**B**). Staining H&E, magnification ×200

cell primary lung tumors had predominantly central localization (Table 1).

No significant differences in tumor size (T1, T2 or T3) were observed among the three groups of the study (Fig. 3).

The incidence of lymphogenous metastasis was significantly higher in patients with combined basal cell hyperplasia and squamous metaplasia (BCH+SM+, 57%) compared to patients with isolated basal cell hyperplasia (BCH+SM–, 38%; $p = 0.05$) while being similar to the frequency of lymphogenous metastasis in patients with neither (BCH–SM–, 47%) (Fig. 3).

Hematogenous metastases were significantly more typical in patients with isolated basal cell hyperplasia (BCH+SM–, 22%) compared to BCH–SM– (0%; $p = 0.019$) and BCH+SM+ (0%; $p = 0.004$) groups (Fig. 3).

Relapses were significantly more typical in patients with combined basal cell hyperplasia and squamous metaplasia (14%) compared to BCH–SM– (0%; $p = 0.05$) and BCH+SM– (2%; $p = 0.02$) groups (Fig. 3).

In the group of patients with neither basal cell hyperplasia nor squamous metaplasia (BCH–SM–, group a), histological type of the tumor was significantly skewed towards adenocarcinoma (65%) as opposed to squamous cell carcinoma (35%; $p = 0.04$). A reciprocal trend was observed for patients with combined basal cell hyperplasia and squamous metaplasia (BCH+SM+, group c) with the prevalence of squamous cell carcinoma (64%) over adenocarcinoma (36%; $p = 0.01$). In patients with isolated basal cell hyperplasia (BCH+SM–, group b) the two histological types of non-small cell lung cancer were encountered at similar frequencies.

The degree of tumor differentiation for adenocarcinoma was similar in all groups. At that, the occurrence of acinar structures in the parenchymal component of adenocarcinoma was significantly lower in patients with isolated basal cell hyperplasia (BCH+SM–, 21%) compared to BCH–SM– (91%; $p = 0.0005$) and BCH+SM+ (90%; $p = 0.0007$) groups. By contrast, papillary structures were extremely typical for adenocarcinoma in BCH+SM– group (100%) and much less so in BCH–SM– (18%; $p = 0.0000$) and BCH+SM+ (20%; $p = 0.0000$) groups. The occurrence of solitary cell patterns in the parenchymal component of adenocarcinoma in BCH+SM+ group was significantly lower (20%) than in BCH–SM– (64%; $p = 0.028$) and BCH+SM– (58%; $p = 0.030$) groups.

The degree of tumor differentiation for squamous cell carcinoma was also similar in all groups. At the same time, architecture of the parenchymal component in squamous cell carcinoma revealed significant associations with morphological changes to the bronchial epithelium. For instance, type II structures (spinous) in the parenchymal component of squamous cell carcinoma were highly typical in BCH+SM+ group (94%) and less so in BCH–SM– (67%; $p = 0.04$) and BCH+SM– (69%; $p = 0.02$) groups.

The occurrence of type III structures (basaloid) in the parenchymal component of squamous cell carcinoma in patients with combined basal cell hyperplasia and squamous

Table 1. Clinical and morphological characterization for the groups of patients with non-small cell lung cancer distinguished on the basis of morphological changes to the bronchial epithelium

Parameter		Groups of the study		
		BCH–SM– ($n = 17$)	BCH+SM– ($n = 45$)	BCH+SM+ ($n = 28$)
		a	b	c
1	Age, M ± SD	59.7 ± 5.3	58.4 ± 8.3	60.5 ± 6.1
2	Sex, a.v., %			
3	Men	14/17 (82%) $p_4 = 0.0001$	36/45 (80%) $p_4 = 0.0000$	25/28 (89%) $p_4 = 0.0000$
4	Women	3/17 (18%)	9/45 (20%)	3/28 (11%)
5	Localization, a.v., %			
6	Central	14/17 (82%) $p_7 = 0.0001$	30/45 (67%) $p_7 = 0.0006$	23/28 (82%) $p_7 = 0.000$
7	Peripheral	3/17 (18%)	15/45 (33%)	5/28 (18%)

Note: a.v. — absolute value; p_4 measures the consistency of equal morbidity hypothesis for men (row 3) and women (row 4) in a given group; p_7 measures the consistency of equal probability hypothesis for central vs peripheral localization (rows 6 and 7, respectively) in a given group.

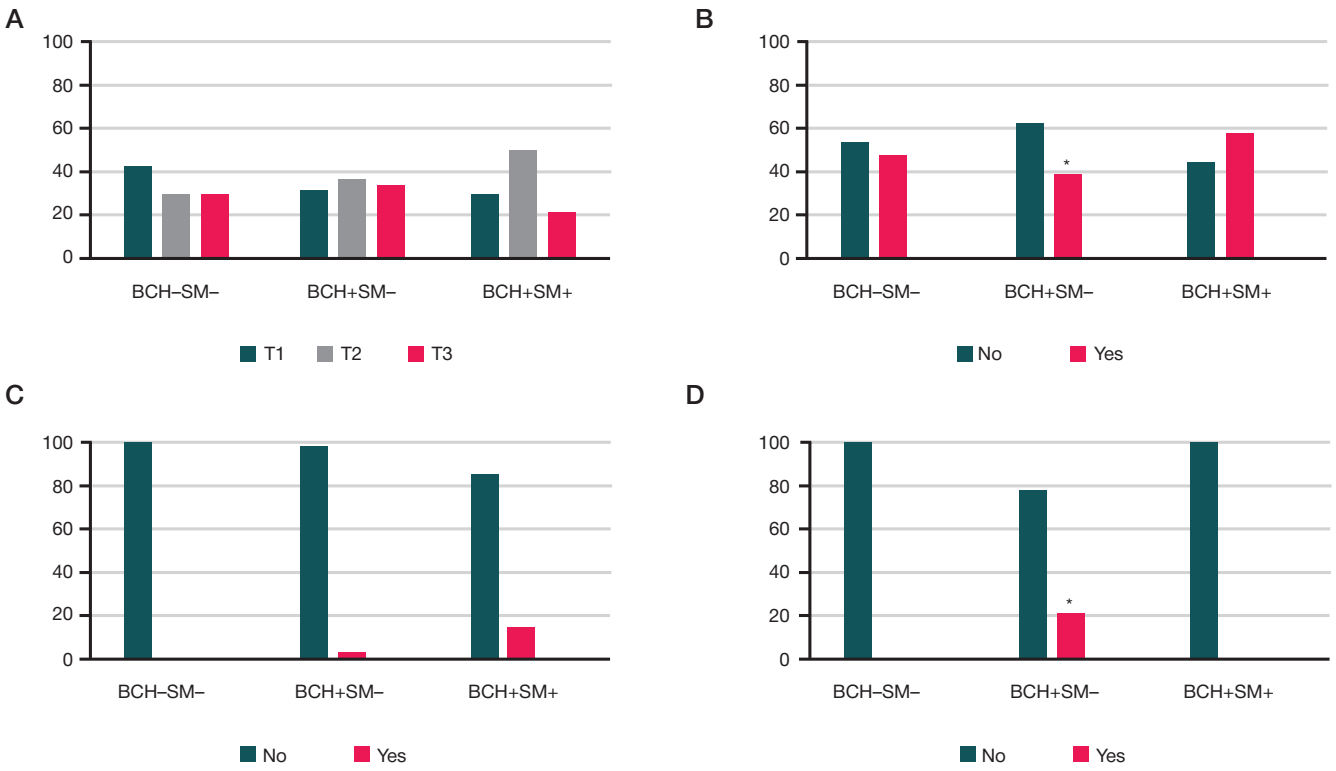

Fig. 3. Comparative characterization of the disease progression indicators in the groups of patients with non-small cell lung cancer distinguished on the basis of morphological changes to the bronchial epithelium. **A**. Tumor size (T). **B**. Lymphogenous metastases. **C**. Relapses. **D**. Hematogenous metastases

metaplasia (BCH+SM+, 22%) was significantly lower than in patients with isolated basal cell hyperplasia (BCH+SM–, 50%; $p = 0.025$) while being similar to the occurrence of such structures in patients with neither (BCH–SM–, 50%).

The three groups of patients revealed similar numbers of structural patterns of the parenchymal component combined in a single tumor and similar degrees of stromal development and inflammatory infiltration for both adenocarcinoma and squamous cell carcinoma (Table 2).

DISCUSSION

The study enabled the identification of characteristic clinical and structural features of non-small cell lung carcinoma in patients with particular morphological changes to the bronchial epithelium.

The group of patients with isolated BCH in the respiratory epithelium of small bronchi outside the tumor (BCH+SM–) showed increased rates of hematogenous metastasis and decreased rates of lymphogenous metastasis. In this group, representation of main histological subtypes of epithelial malignancy (adenocarcinoma, squamous cell carcinoma) was balanced. Adenocarcinomas diagnosed in patients with isolated BCH typically presented with low-differentiated papillary structures and, less typically, with higher differentiated acinar structures.

The group of patients with combined BCH and SM in the respiratory epithelium of small bronchi outside the tumor (BCH+SM+) showed increased rates of lymphogenous metastasis and recurrence against the lack of hematogenous metastasis. The prevalent diagnosis in this group was squamous cell carcinoma, most commonly of type II (spinous, higher differentiated) and less commonly of type III (basaloid, lower differentiated).

By contrast, the prevalent diagnosis in patients with neither BCH nor SM (BCH–SM–) was adenocarcinoma. The incidence of adverse manifestations (lymphogenous and hematogenous metastasis, relapses) and morphological variations of the tumor architecture in this group were regular.

Of note, patients of BCH+SM+ group presented with lymphogenous metastases more frequently than patients of BCH+SM– group. The majority of relapses in non-small cell lung cancers are due to metachronous lymphogenous metastasis [14]. Our results indicate the existence of intersecting links in the mechanisms of synchronous and metachronous lymphogenous metastasis.

The higher incidence of hematogenous metastasis in BCH+SM– group and the higher incidence of relapses in BCH+SM+ group are consistent with previously reported findings. The data indicate that these groups significantly differ not only by the structure of clinical risks, but also by morphological features of the primary tumors. Interestingly, in BCH+SM+ group, the prevalent histological type was squamous cell carcinoma. The susceptibility to squamous metaplasia under conditions of chronic inflammation augments the development of squamous cell carcinoma, as the metaplastic squamous epithelium provides a favorable site for the pre-cancer dysplasia capable of progression into carcinoma. The associated differences in morphological architecture of primary tumors, reported for the first time herein, appear even more relevant. Consistently with the higher risks of hematogenous metastasis, BCH+SM– group shows increased occurrence of low-differentiated structures in both adenocarcinoma and squamous cell carcinoma. The differential character of epithelial changes in small bronchi most likely reflects some essential, constitutive differences in the stromal-parenchymal relationships inextricably linked to the parenchymal-stromal interactions in the adjacent carcinomas [13, 14].

The observed among-the-group differences in the condition of the stroma are obviously based on the features of immune and inflammatory reactions. The results allow us to assume that the mode of inflammatory response delivered by microenvironment of non-small cell lung cancer with isolated basal cell hyperplasia

Table 2. Histological characterization of the primary tumors for the groups of patients with non-small cell lung cancer distinguished on the basis of morphological changes to the bronchial epithelium

Parameter		Group of the study		
		BCH–SM– (n = 17)	BCH+SM– (n = 45)	BCH+SM+ (n = 28)
		a	b	c
1	Histological type, a.v., %			
2	Adenocarcinoma	11/17 (65%) p_3 = 0.04	19/45 (42%)	10/28 (36%) p_3 = 0.01
3	Squamous cell carcinoma	6/17 (35%)	26/45 (58%)	18/28 (64%)
4	Degree of tumor differentiation in adenocarcinoma, a.v., %			
5	High	3/11 (27%)	7/19 (37%)	2/10 (20%)
6	Medium	5/11 (46%)	7/19 (37%)	5/10 (50%)
7	Low	3/11 (27%)	5/19 (26%)	3/10 (30%)
8	Structural patterns in adenocarcinoma, a.v., %			
9	Lepidic	2/11 (18%)	7/19 (37%)	2/10 (20%)
10	Acinar	10/11 (91%)	"4/19 (21%) pa = 0,0005 pc = 0,0005"	9/10 (90%)
11	Papillary	2/11 (18%)	19/19 (100%)	2/10 (20%)
12	Micropapillary	3/11 (27%)	7/19 (37%)	1/10 (10%)
13	Solid	6/11 (54%)	6/19 (32%)	5/10 (50%)
14	Solitary cells	7/11 (64%)	11/19 (58%)	2/10 (20%)
15	Number of structural patterns combined in a single tumor for adenocarcinoma, Me ($Q_1 \div Q_3$)	3.0 (2.0÷3.0) (n = 11)	3.0 (2.0÷4.0) (n = 19)	2.0 (1.0÷3.0) (n = 10)
16	Overall representation of stromal component in adenocarcinoma, points, Me ($Q_1 \div Q_3$)	1.0 (1.0÷2.0) (n = 11)	1.0 (1.0÷2.0) (n = 19)	2.0 (1.0÷2.0) (n = 10)
17	Overall degree of inflammatory stromal infiltration in adenocarcinoma, %, Me ($Q_1 \div Q_3$)	20.0 (10.0÷90.0) (n = 11)	20.0 (10.0÷60.0) (n = 19)	15.0 (10.0÷60.0) (n = 10)
18	Degree of tumor differentiation in squamous cell carcinoma, a.v., %			
19	High	0/6 (0%)	2/26 (8%)	0/18 (0%)
20	Medium	4/6 (67%)	17/26 (65%)	12/18 (67%)
21	Low	2/6 (33%)	7/26 (27%)	6/18 (33%)
	Structural patterns in squamous cell carcinoma, a.v., %			
22	Type I (keratinized)	0/6 (0%)	6/26 (23%)	2/18 (11%)
23	Type II (spinous)	4/6 (67%)	18/26 (69%)	17/18 (94%) p_a = 0.04 p_b = 0.02
24	Type III (basaloid)	3/6 (50%)	13/26 (50%) p_c = 0.025	4/18 (22%)
25	Type IV (polymorphous)	2/6 (33%)	14/26 (54%)	11/18 (61%)
26	Solitary cells	3/6 (50%)	17/26 (65%)	9/18 (50%)
27	Number of structural patterns combined in a single tumor for squamous cell carcinoma, Me ($Q_1 \div Q_3$)	2.0 (1.0÷3.0) (n = 6)	3.0 (1.0÷4.0) (n = 26)	2.5 (1.0÷3.0) (n = 18)
28	Overall representation of stromal component in squamous cell carcinoma, points, Me ($Q_1 \div Q_3$)	1.5 (1.0÷2.0) (n = 6)	2.0 (1.0÷2.0) (n = 26)	1.0 (1.0÷2.0) (n = 18)
29	Overall degree of inflammatory stromal infiltration for squamous cell carcinoma, %, Me ($Q_1 \div Q_3$)	40.0 (20.0÷70.0) (n = 6)	20.0 (10.0÷70.0) (n = 26)	20,0 (5.0÷70.0) (n = 18)

Note: p_3 measures the consistency of equal probability hypothesis for squamous cell carcinoma (row 3) and adenocarcinoma (row 2) in a given group; p_a measures the consistency of differences in a given parameter with group a (BCH–SM–); p_b measures the consistency of differences in a given parameter with group b (BCH+SM–); p_c measures the consistency of differences in a given parameter with group c (BCH+SM+).

of the bronchial epithelium outside the tumor (BCH+SM–) facilitates not only hematogenous metastasis but also de-differentiation of the tumor elements. The latter effect may act as an autonomous factor contributing to hematogenous metastasis. Deciphering the mechanisms of this contribution will require further research activities.

CONCLUSIONS

The study evaluates the condition of lung parenchyma in the vicinity of malignant epithelial tumors. The results confirm the association of specific morphological changes to the epithelium in small bronchi with the risks of metastasis

and recurrence, while further associating these changes with the degree of tumor differentiation. The identified trends may reflect some universal, constitutive features of stromal-parenchymal interactions that equally apply to pulmonary chronic inflammation and tumorigenesis. Detailed examination of histochemical and molecular genetic mechanisms that define and elaborate these interactions is a matter of further research.

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