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FEATURES OF CD4+, CD8+ LYMPHOCYTES DISTIRBUTION IN SQUAMOUS CELL LUNG CARCINOMA

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Exploring the features of lung cancer microenvironment is of particular interest now. Immunocytes present the main component of tumor microenvironment and also form the separate unit of oncogenesis [1-2]. It was proved, that tumor-associated immunocytes have an influence on the survival of tumor cells, the processes of proliferation and apoptosis, the realization of metastatic cascade [3]. Several studies have shown that an increase of T-lymphocytes number in tumor complexes, as well as in peritumorous stroma, is associated with the better prognosis for patients, suffered from melanoma, breast carcinoma, head and neck cancer [4]. G. A. Banat et al. (2015) established that the CD4+, CD8+, CD20+, CD68+ immunocytes number in lung cancer tissue is higher, than in normal tissue, that is associated with an implementation of antitumor response by immune system [2]. But the question of the significance of immunocytes distribution in the lung cancer is still open.

Aim – to characterize the features of CD4+, CD8+ lymphocytes distribution in non-metastatic squamous cell lung carcinoma and squamous cell lung carcinoma with regional metastases.

Materials and methods. Pathomorphological and immunohistochemical studies of the operational material from 20 patients with squamous cell lung carcinoma (SCLC) were conducted. The first study group was formed of the material from 10 patients with non-metastatic SCLC ($pT_{1-2}N_0M_0G_{1-3}$), while the second study group was formed of the material from 10 patients with metastatic SCLC ($pT_{1-2}N_{1-2}M_0G_{1-3}$).

IHC study was performed using the monoclonal mouse antibodies CD4 Clone MT310, CD8 T-Cell Clone C8/144B («DAKO», Denmark) and visualization system DAKO EnVision+ with diaminobenzidine («DAKO», Denmark). The results of the study were evaluated in the Axioplan 2 microscope («Carl Zeiss», Germany), microsections were photographed by digital camera «Canon EOS 1000D» (Japan) with increasing of x200 in 5 fields of view. The quantitative analysis of the immunocytes distribution (in the tumor complexes, the peritumorous and intertumorous zones of the tumor stroma) was conducted. The division of the tumor stroma into the peritumorous and intertumorous zones is based on the literature data, ac-

cording to which immune responses are more intense in the stromal regions, that immediately adjacent to the tumor complexes [4]. To conduct the calculations, the Photoshop CC (2014) was used.

Statistical processing of the results was performed on a personal computer using program «STATISTICA® for Windows 6.0» (StatSoft Inc., License № AXXR712D833214FAN5). The density of the immunocytes distribution was calculated per square millimeter. The median (Me), the lower and the upper quartiles (Q_1; Q_3) were calculated. Comparison was performed using Mann-Whitney U-test. The difference was considered as statistically significant when $p<0,05$.

Results. The median values of the CD4+ lymphocytes distribution density in the tumor complexes are 13,5 (2,0; 26,9) cells/mm^2 for non-metastatic SCLC and 34,8 (0,0; 52,3) cells/mm^2 for SCLC with metastases in the regional lymph nodes. The same figures are significantly different in the tumor stroma: in the intertumorous zones of non-metastatic SCLC – 298,0 (246,1; 350,1) cells/mm^2, metastatic SCLC – 484,8 (479,3; 690,6) cells/mm^2; in the peritumorous zones of non-metastatic SCLC – 401,2 (344,6; 511,3) cells/mm^2, metastatic SCLC – 622,4 (587,2; 793,9) cells/mm^2. Thus, it was revealed, that the minimum CD4+ lymphocytes distribution density takes place in the tumor complexes of SCLC and the maximum – in the peritumorous zones. Statistically significant differences between the medians of CD4+ lymphocytes distribution density in the different stroma's zones of non-metastatic and metastatic SCLC were revealed: for the intertumorous zones the U-criterion is 16.0 (p=0.011), for the peritumorous zones – 17.0 (p=0.014). Thus, it was revealed, that SCLC with metastases in the regional lymph nodes is characterized by the higher CD4+ lymphocytes distribution density in the stroma compared with non-metastatic SCLC.

The similar pattern of CD8+ lymphocytes distribution was revealed: the minimum distribution density takes place in the tumor complexes of SCLC and the maximum – in the peritumorous zones. The median values of the CD8+ lymphocytes distribution density in the tumor complexes are 52,7 (36,0; 126,9) cells/mm^2 for non-metastatic SCLC and 77,0 (38,2; 110,7) cells/mm^2 for SCLC with metastases in the regional lymph nodes. The same figures in the intertumorous stroma's zones of non-metastatic SCLC is 327,0 (294,9; 400,9) cells/mm^2, metastatic SCLC – 302,3 (193,8; 490,0) cells/mm^2; in the peritumorous zones of non-metastatic SCLC – 371,5 (283,7; 437,5) cells/mm^2, metastatic SCLC – 391,123 (270,1; 452,9) cells/mm^2. Although there is the expressive tendency to increase the values of the CD8+ lymphocytes distribution density in metastatic SCLC, there are no statistically significant differences: U-criterion for the tumor complexes of SCLC is 43,0 (p=0,623), U-criterion for the intertumorous and peritumorous zones is 49,0 (0,970).

Discussion. Well known that CD4+ T-lymphocytes play an important role in the process of the antitumor immune response: they activate cytotoxic CD8+ cells, inhibit tumor angiogenesis. CD8+ T-lymphocytes, in its turn, in response to the

recognition of tumor-associated antigens, produce cytotoxic mediators that act directly on the tumor complexes [5-6].

The value of the CD8+ T-lymphocytes distribution density in the tumor complexes is significantly higher than the same value for CD4+ T-lymphocytes, that associate with the function of CD8+ subpopulation. However, despite the significant number of CD4+ and CD8+ immunocytes in the tumor microenvironment, the possibility of modifying their properties should be considered. Several studies have shown the increase of intensity of immune cell infiltration with the lung cancer progression [2, 7-10]. Probably, the tumor-associated cytokines also have an effect on T-lymphocytes, inhibiting their antitumor properties. It is possible to acquiring by immunocytes some new properties, that promote tumor progression [7].

The literature data about the features of CD4+, CD8+ immunocytes distribution in lung cancer varies, but it agrees with our results on the general principle: the number of immunocytes in the tumor stroma is much higher than that in the tumor complexes [2, 5, 8-10]. The higher immunocytes distribution density in the tumor stroma, compared with the same values for the tumor complexes, indicates greater activity of antitumor cytokines in the stromal component of the tumor.

Conclusions.

1. The minimum CD4+, CD8+ lymphocytes distribution density take place in the tumor complexes of squamous cell lung carcinoma and the maximum – in the peritumorous zones of squamous cell lung carcinoma.
2. Squamous cell lung carcinoma with regional metastases is characterized by the higher CD4+ lymphocytes distribution density in the stroma compared with non-metastatic squamous cell lung carcinoma.

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ПРИХИЛЬНІСТЬ ДО ЛІКУВАННЯ ЯК ВАЖЛИВА СКЛАДОВА ЕФЕКТИВНОЇ ТЕРАПІЇ БРОНХІАЛЬНОЇ АСТМИ

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Бронхіальна астма (БА) є важливою медичною, соціальною та економічною проблемою сьогодення, оскільки вона призводить до втрати працездатності та порушення якості життя (ЯЖ) пацієнтів [1, с. 51; 3, с.13; 5]. Від астми страждає майже 300 мільйонів людей у світі та щорічно помирає близько 250 000 осіб. Не зважаючи на велику кількість препаратів, які використовуються у лікуванні астми, досягти контролю над хворобою дуже важко [1, с. 52; 4, с. 202]. Дані бага-