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DOI: 10.20969/VSKM.2019.12(6).22-28
computed tomography (HR-CT) Doppler echocardiography (Doppler-Echo) we characterized the biomarkers directly identifying the risk for development of PAH in patients with chronic lung tuberculosis, detection of cellular immune response. The risk for development of PAH in patients was learned by assessing of proinflammatory cytokines (IL-6, TNF-α) and proinflammatory peptides (CRP, NT-pro BNP). Depends on volume of irreversible morphological changes related lung tuberculosis all patients were divided in two groups: 1) 26 patients with CDLT+COPD and with PAH, 2) 25 patients with CDLT+COPD without PAH, 12 practically healthy individuals served as controls. All patients have been admitted to the Departments of Medical University. Results and discussion. Our data reveal that proinflammatory cytokines (IL-6, TNF-α) and proinflammatory peptides (CRP, NT-pro BNP) may play role as predictors for assessment of development severity of PAH in patients with CDLT+COPD. Our study also shown that the high level of proinflammatory cytokines and peptides were associated with more severe PAH in patients. In CDLT+COPD, lung parenchyma, bronchi vessels is involved in complex processes coupling the bronchopulmonary and cardiovascular systems. Conclusions. Chronic lung inflammation with elevation of the level proinflammatory cytokines and peptides have critical contribution of lung parenchyma, bronchi and vessels remodeling and the fringe of nonreversible morphological changes in the lung at PAH in CDLT+COPD.

Key words: chronic obstructive pulmonary disease, chronic destructive lung tuberculosis, pulmonary arterial hypertension, cellular immune response, diastintest, proinflammatory cytokines and peptides.

For reference: Ismailzade JM, Bayramov RI, Gurbanova ZT, Kadimova ZSh, Nagiyeva UB, Ibragimov TG. Clinical features of pulmonary arterial hypertension in patients with chronic destructive lung tuberculosis combined with chronic obstructive pulmonary disease. The Bulletin of Contemporary Clinical Medicine. 2019; 12 (6): 22-28. DOI: 10.20969/VSKM.2019.12(6).22-28.
One of the most common symptoms of chronic and persistent lung tuberculosis is dyspnea [5]. In such patients, together with irreversible morphological changes in lung tissue (parenchyma) these changes may affect also lung vascularity and may developed vascular remodeling in pulmonary arteries [6]. This mechanism together with hypoxic vasoconstriction may play important role for development in of PAH in such patients [7, 8]. PAH is an established complication of CDLT and COPD [9, 10] and they have been demonstrated to be an independent risk factors for death [11]. Its prevalence depends on severity of irreversible morphological changes in lung parenchyma, and PAH typically occurs in a subpopulation of patients with CDLT and COPD with significantly morphological changes, when ventilation perfusion mismatching is severe and associated with hypoxia [12, 13]. During reference analysis we identified limited data related with some biomarkers which may play role as predictor for development and severity of PAH in patients with CDLT+COPD.

The aim of the present study was to describe the clinical, biomarkers and computed tomography (CT) characteristics of patients with CDLT+COPD with or without PAH.

Material and methods. Data were retrieved from all consecutive patients with CDLT+COPD older than 40 years of age who were referred to the tertiary unit of our university between January 2012 and May 2017 for complete examination of chronic respiratory failure and treatment. The study was performed in accordance with the ethical standards of the bioethical committee, developed in accordance with the Helsinki Declaration of the World Medical Association «Ethical Principles of Medical Research Involving Human Subjects» with the amendments of 2013 and the «Rules of Ethical Conduct of Medical Workers» approved by the Order (№ 137) of the Ministry of Health of the Republic of Azerbaijan dated 29.12.2011. The patients and persons of control group had to undergo a standardized panel of investigations, including carefully assembled histories, physical examinations, X-ray examination, explored the peripheral blood (complete blood count) and sputum examination on the presence of AFB. Detection of cellular immune response carried out using Diaskintest based on an evaluation of delayed-type hypersensitivity. We used the interdermal injection of Diaskintest at a dose of 2 mkg in 0,1 ml, containing ESAT6-CFP10 (Lecoe, Russia) present in virulent strains of MBT. The reactions were evaluated visually after 72h and measured the size of induration in millimeters. The result were considered negative in the absence of infiltration, doubtful if hyperemia without infiltration, positive if there is infiltration (papules) of any size, hyperergic when the diameter of infiltration 15 mm and more, formation vesicle and necrosis and (or) the presence of lymphangitis, lymphadenitis. pulmonary...
The principle behind the method for determining the amount of CRP in a blood serum is based on the creation of an immune complex against it using the antibodies in a specific serum (latex reagent). This is accompanied by a visible agglutination of a latex reagent (Human, Germany).

The NUP concentration was determined with the help of a standard reagent kit produced by Human (Germany). This was carried out by using two-site, noncompetitive immunoassays method (also known as «sandwich» type immunoassay) (N-terminal pro-B-type natriuretic peptide, NT Pro-BNP).

The principle of the method is based on the interaction, in a patient’s blood serum, between monoclonal mouse antibodies that cover the walls of the test tube of free NT pro-BNP and biotinized polyclonal rabbit antibodies prepared against the human NUP and the combination of alkaline phosphatase and conjugated streptavidin.

The results were evaluated by measuring the intensity of the color produced by conjugation with a specific chromogen (chromogenic substrate).

To compare and determine the significance of differences of quantitative values in paired groups, non-parametric Wilcoxon test was used (Mann-Whitney), and between multiple groups, Kruskal-Wallis test. The correlations between the studied parameters were defined using Spearman criterion. The calculations were performed using SPSS-20 software package.

**Results and discussion.** A total of 51 patients with CDLT met the inclusion and exclusion criteria. Demographic, respiratory function, biologic and hemodynamic data of the study population are presented in table 1.

There was no difference between CDLT+COPD patients with \(n=26\) and those without PAH \(n=25\) regarding age and sex ratio. In the comparison groups

**Table 1**

| Characters                  | CDLT with COPD, without PAH \((n=25)\) | CDLT+COPD with PAH \((n=26)\) | Control \((n=12)\) | \(p\) value |
|-----------------------------|----------------------------------------|-------------------------------|-------------------|-------------|
| **Sex, m/f**                | 20 / 5                                 | 18 / 8                        | 9 / 3             | 0.677       |
| **Age, year**               | 45.2±2.5 \ ((29-69) \])               | 44.7±2.2 \ ((29-69) \])     | 43.2±3.2 \ ((25-59) \]) | 0.905       |
| **Diaskintest**             | Positive                               | Positive                      | Negative          |             |
| **Dyspnea, mMRCs**          | 0.92±0.14 \ ((0-2) \])               | 3.3±0.23 \ ((1-5) \)         | 0.50±0.15 \ ((0-1) \) | < 0.001     |
| **FEV1, %**                 | 69.7±1.3 \ ((58.1 – 78.4) \)***     | 68.4±1.1 \ ((56.6 – 77.9) \)**** | 93.3±1.0 \ ((89-99) \) | < 0.001     |
| **FVC, %**                  | 59.4±1.5 \ ((45 – 67) \)***          | 47.3±1.4 \ ((36 – 59) \)**** | 99.2±1.6 \ ((90-106) \) | < 0.001     |
| **FEV1/FVC**                | 98.1±2.2 \ ((79.3-123.9) \])        | 65.8±1.1 \ ((55 – 74.7) \) | 94.3±1.6 \ ((84.8-100.0) \) | 0.430       |
| **RV1, %**                  | 68.4±2.67 \ ((58 – 79) \) **         | 82.9±1.0 \ ((72-90) \)     | 94.9±0.8 \ ((90-99) \) | < 0.001     |
| Characters                      | CDLT with COPD, without PAH (n=25) | CDLT+COPD with PAH (n=26) | Control (n=12) | p value |
|--------------------------------|------------------------------------|---------------------------|---------------|---------|
| TLC, %                         | 80,6±1,3 (68-93) ***               | 70,7±1,6 (60-86) ******   | 89,3±1,3 (84-96) | <0,001  |
| DLco, %                        | 65,4±1,4 (54-76) ***               | 48,8±1,6 (33-61) ******   | 88,8±1,3 (82-96) | <0,001  |
| Arterial blood gases (room air) |                                    |                           |               |         |
| PaO₂, mm Hg                    | 76,3±1,5 (65-92) ***               | 56,2±2,2 (36-75) ******   | 94,3±1,0 (86-98) | <0,001  |
| PaCO₂, mm Hg                   | 42,6±0,6 (37-46) **                | 43,0±1,3 (32-55)         | 39,6±0,8 (36-45) | 0,071   |
| Biological tests               |                                    |                           |               |         |
| CRP, mg/ml                     | 13,2±0,6 (6-19) ***                | 19,5±1,4 (8-32) ******    | 2,9±0,3 (1-2,4) | <0,001  |
| II-6, pg/ml                    | 27,3±1,9 (15,6-45,6) ***           | 38,2±1,9 (20,1-59,2) ****** | 14,2±2,8 (2,9-30,6) | <0,001  |
| TNFa, pg/ml                    | 69,3±1,7 (59-85) ***               | 86,1±3,4 (60-137) ******  | 35,3±5,4 (11-67) | <0,001  |
| NTproBNP, ng/ml                | 652,8±44,2 (390-1000) *            | 874,8±77,2 (380-1800) *** | 490,3±48,0 (340-785) | 0,001   |
| LVEF (echo), %                 | 54,3±0,7 (49-62)                    | 63,8±1,6 (49-77) ****** | 52,9±0,8 (49-58) | <0,001  |
| RHC                            |                                    |                           |               |         |
| PAPs, mm/Hg                    | 36,2±2,2 (25-48) **                | 45,6±1,0 (39-50) ******   | 25,0±0,9 (29-29) | <0,001  |
| PAPm, mm/Hg                    | 27,4±1,3 (21-34) ***               | 32,0±1,4 (24-38) ******  | 13,7±0,7 (12-16) | <0,001  |
| PAPd, mm/Hg                    | 15,7±1,4 (9-23) **                 | 20,3±1,7 (12-28) ******  | 9,8±0,7 (7-12) | 0,001   |
| PVR, w.u.                      | 3,1±0,16 (2-3,7) **                | 4,2±0,28 (2-9,5) ******   | 2,3±0,14 (2-2,9) | 0,001   |
| PCWP, mm/Hg                    | 6,0±0,22 (4-9,2) **                | 6,6±0,21 (5-9,7) ******   | 4,7±0,18 (4-5,2) | 0,001   |
| CI, L/min/m²                   | 2,89±0,06 (2,6-3,2)               | 2,92±0,07 (2,6-3,3)    | 3,1±0,09 (2,8-3,4) | 0,085   |
| AP/AO                          | 0,84±0,021 (0,75-0,96) *           | 0,98±0,021 (0,86-1,06) ****** | 0,75±0,017 (0,7-0,8) | <0,001  |

Note: 1) a statistically significant difference (U-Wilcoxon (Mann – Whitney): – with the control group: *p<0,05; **p<0,01; ***p<0,001; – with indicators of Group without PAH: *p<0,05; **p<0,01; ***p<0,001; 2) a statistically significant difference between groups (Kruskal – Wallace) – p value.

Definition of abbreviations: CDLT-chronic destructive lung tuberculosis; LVEF-left ventricular ejection fraction; mMRCs – modified Medical Research Council scale; PAPd = diastolic pulmonary arterial pressure; PAPm = mean pulmonary arterial pressure; PAPs = systolic pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PAH = pulmonary arterial hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = residual volume; TLC = total lung capacity; DLco = transfer lung capacity of carbon monoxide. AP/AO = diameter ratio between the pulmonary arterial truncus and the ascending aorta.

(CDLT with COPD without PAH and CDLT+COPD with PAH) no one had discovered negative anergy. In both groups of comparison, different intensity, positive reactions to Diaskintest were revealed. Negative Diaskintest was detected in all persons belonging to the control group. The FEV1 was also not significantly different. DLco measurement was significantly less in patients with PAH (p<0,001) which suggested about more markedly affecting area of lung (two and more pulmonary lobes) with non reversible morphological changes. Hypoxemia was more severe in patients CDLT+COPD with PAH.

At the vascular level, the diameter ratio between the pulmonary arterial truncus and the ascending aorta (AP/AO) was higher in patients with CDLT+COPD with PAH (p<0,001). It suggested that in such patient’s chronic destructive lung tuberculosis non reversible morphological changes are not single mechanism for development of PAH.

When we assessed each CDLT+COPD population with and without PAH separately, as well as the whole study population, we found that positive correlation coefficients between PAPm and the extent of non reversible morphological changes in the lung parenchyma (table 2).

The analysis of proinflammatory cytokines and peptides shown positive correlation between these and the level of mPAP (Figure). More significantly elevation of mPAP was noted in patients with NT-pro BNP level more than 500 ng/ml.
Correlations between mean pulmonary arterial pressure (PAPm) and NTproBNP in patients with CDLT+COPD

| Characters | TLC | PO2 | CRP | Il-6 | proBNP | PAPm | AP/AO |
|------------|-----|-----|-----|------|--------|------|-------|
| TLC        |     |     |     |      |        |      |       |
| r          |   0.411** |     | -0.200 | -0.471** | -0.322* | 0.131 | -0.085 |
| p          |     |     |     |      |        |      |       |
| PaO2       |     |     |     |      |        |      |       |
| r          |   -0.225 | -0.508** | -0.203 | -0.094 | -0.649** |     |       |
| p          |     |     |     |      |        |      |       |
| CRP        |     |     |     |      |        |      |       |
| r          |     |   0.363** | 0.114 | 0.282 | 0.597** |     |       |
| p          |     |     |     |      |        |      |       |
| Il-6       |     |     |     |      |        |      |       |
| r          |     |     |     |      |        |      |       |
| p          |     |     |     |      |        |      |       |
| NTproBNP   |     |     |     |      |        |      |       |
| r          |     |     |     |      |        |      |       |
| p          |     |     |     |      |        |      |       |
| PAPm       |     |     |     |      |        |      |       |
| r          |     |     |     |      |        |      |       |
| p          |     |     |     |      |        |      |       |

Note: Correlation is significant (2-sided) at the level: *p<0.05; **p<0.01.

Correlations between mean pulmonary arterial pressure (PAPm) and NTproBNP in patients with CDLT+COPD with and without PAH

Our results may indicate that, using relevant information related to vessels (AP/AO), extent of nonreversible morphological changes in lung, hypoxia (PaO2), and more important to NTpro-BNP level, a multivariate model can improve this alternative strategy to estimate PAPm noninvasively.

Finally, our results give evidence that in CDLT+COPD, lung parenchyma, bronchi vessels is involved in complex processes coupling the bronchopulmonary and cardiovascular systems. This may provide further understanding of the burden of lung parenchyma and airway remodeling to explain CDLT+COPD severity and mortality. Specifically, our study suggests a critical contribution of lung parenchyma, bronchi and vessels remodeling to explain PAH in CDLT+COPD at the fringe of nonreversible morphological changes in the lung, gas exchange, and chronic lung inflammation with elevation of the level proinflammatory cytokines and peptides.

Transparency of the study. The study did not have sponsorship. The authors are solely responsible for the provision of the final version of the manuscript for publication.

Declaration of financial or other relationships. All authors participated in the conception and design of the study and in the writing of the manuscript. The final version of the manuscript was approved by all the authors. The authors did not receive a fee for the study.

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Цель исследования
– изучить динамику количества и объема хирургических операций узловых форм зоба в условиях йодообеспеченности (1984–1990) и йододефицита (1999–2005) в Узбекистане.

Материал и методы.
Представлены данные из историй болезни 4256 больных, оперированных по поводу узлового зоба с 1984 по 2005 г. в НИИ эндокринологии МЗ РУз.

Выводы.
С 1984 по 2005 г. в НИИ эндокринологии МЗ РУз были прооперированы 4256 больных по поводу узлового зоба. В годы йодообеспеченности (1984–1990) количество таких операций было меньше, а в годы йододефицита (1999–2005) наблюдалось их резкое увеличение. Количество более радикальных и агрессивных операций на щитовидной железе при узловом зобе в условиях йододефицита возрастает.

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DOI: 10.20969/VSKM.2019.12(6).28-33