Paraneoplastic rheumatoid-like arthritis associated with lung cancer

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Abstract. Background. Paraneoplastic syndrome (PNPS) associated with lung cancer (LC) is characterized by rheumatological, dermatological, endocrinological, neurological, nephrological and other manifestations. PNPS has become an urgent problem of modern oncology, but specifics of its course and immediate tumor process have not been investigated enough. The purpose was to estimate the clinical laboratory manifestations of paraneoplastic (neoplastic) rheumatoid-like arthritis (RLA) within the context of its associations with LC individual signs. Materials and methods. PNPS was detected in 258 (16%) patients with LC and RLA in 41 (16%) cases of PNPS. These patients (29 men and 15 women with an average age of 57 years) were made up the main group of this study, and other 217 patients with PNPS (177 men and 40 women with an average age of 59 years) were included into the comparison group. Another control group was formed by 105 patients (22 men and 83 women aged 46 years) with primary rheumatoid arthritis (RA) without LC.

Results. LC with RLA is characterized by the accelerated midlobar localization of tumor process (7.4 times more often), its small-cell variant (5.3 times more often) with a low degree of differentiation, the presence of exudative pleurisy, neoplasms germinating into esophagus and metastases growing into the skeleton (pubic, iliac, femoral and sacral bone, jaw and spine). By contrast to the RA, RLA is characterized by oligoarthritis, enthesopathies, seronegativity by the rheumatoid factor and antibodies to cyclic citrulline peptide, less manifested activity and stages of the articular syndrome (by 1/4), higher damage rate of radiocarpal joints (1.8 times), shoulder joints (4.8 times), metacarpal (2.4 times) and metatarsophalangeal (2.5 times) joints, absence of osteousuras, intra-articular chondromic bodies, Steidi and Goff bodies. Conclusions. Formation of paraneoplastic RLA is observed in every sixth patient with PNPS caused by LC, which is accompanied by specific features not only of tumor process, but also by joint syndrome in comparison with the primary RA. The obtained data necessitate the further investigation in order to develop criteria for early diagnosis of RLA and informative prognostic factors for the further course of LC.

Keywords: cancer; lung; paraneoplastic syndrome; arthritis
89% males and 11% females. The right-hand localization of cancer was characteristic of 57% patients, left-hand — of 42%, bilateral — of 1%. The upper lobe LC was diagnosed in 29% cases, middle-upper lobe LC — in 21%, upper-lower left-hand LC — in 20%, lower LC — in 13%, mediastinal LC — in 11%, midlobar — in 3%, middle-lower LC - 2%.

The small-cell histological variant was diagnosed in 19 % cases, while the non-small-cell histological variant — in 82%, among them adenocarcinoma accounted for 37% of all examined cases and 46 % of the non-small-cell cases, planocellular carcinoma — for 35 and 43% respectively, and large-cell carcinoma — for 9 and 11%.

The IB and IIА stages were diagnosed in 1% LC cases, IIВ — in 4%, IIIА — in 35%, IIIВ — in 26%, IV — in 34%. The mean integral stage index (StT) was 5.9±0.03 r.u., integral severity index of tumor process (IWT) - 2.9±0.02 a.u., evaluated according to the formula:

\[ IWT = \ln(T + N^2 + (\Sigma M)^2) \]

where \( \ln \) — natural logarithm, \( T \) - international index of the primary tumor, \( N \) - international index of metastasis in the regional lymph nodes, \( \Sigma M \) - sum of metastases in the distant organs. Among the LC signs, 10% reported exudative pleurisy, 8% —compression syndrome, 7% — tracheal invasion, 3% - rib and chest wall invasion, respectively, 2% - esophageal invasion, 1% — pericardial invasion. 4% cases had obstructive atelectasis, 3% — compression of the recurrent nerve, 2% - compression of the upper vena cava. Metastatic spreading of LC to lymph nodes was found in 81% of observations, to distant organs — in 31%, to the skeleton — in 20%.

Among all the LC patients, a principal group of paraneoplastic (neoplasmic) rheumatoid-like arthritis (RLA) patients was recruited (79 patients, i.e. 5%), while the control group was made out of the remaining patients with no PNPS signs. The RLA course was compared with the classic “primary” RA course of 105 patients, matched for age, sex and duration (second control group). In order to diagnose LC and its metastases, we used radiography, computed tomography, magnetic resonance imaging (Multix-Compact—Siemens, Germany; Somazom-Emotion—6—Siemens, Germany; Gygoscan-Intera—Philips, Netherlands; cyclotron Siemens-RDS-Eclipse—RD, Germany), fibroscope (Olympus-GIF-Q20, Japan), sonograph (Envisor-Philips, Netherlands).

Statistical analysis of the data was carried out using computer variational, nonparametric, correlative, one- (ANOVA) and multifactorial (ANOVA/MANOVA) dispersion analysis (Microsoft Excel and Statistica—Stat-Soft, USA). Mean values (M), their standard deviations (SD) and errors (SE), Pearson’s parametric correlation coefficients (r) and Kendall’s non-parametric correlation coefficients (τ), even dispersions of Brown — Forsythe (BF), multivariate dispersion of Wilcoxon — Rao (WR), Student (t)and McNemar — Fisher’s (χ²) tests, and the reliability of statistical indices (p) were estimated. In this study, the critical level of significance in terms of statistical hypotheses’ verification was considered to be 0.05. The positive predictive value (PPV) was also calculated.

**Results**

The principal (I) group of RLA patients and control (II) group with no PNPS did not differ in terms of age, side of tumor affection and form of disease (central, peripheral). However, in the principal (I) group lower-lobe LC localization was 6.9 times rarer (\( \chi^2=5.62, p=0.02 \)), while mediastinal LC — 6.0 times rarer (\( \chi^2=4.45, p=0.04 \)); midlobar LC — 7.4 times more frequent (\( \chi^2=16.96, p<0.001 \)), while the small-cell histological variant — 5.3 more frequent.

![Fig. 1. Differences of joint disorder frequencies in the principal and control group](image-url)

**Joints:**
1. metacarpophalangeal, 2 — interphalangeal (manus), 3 — metatarsophalangeal, 4 — radiocarpal, 5 — glenohumeral, 6 — maxillary, 7 — talocrural, 8 — interphalangeal (pedis), 9 — knee, 10 — sternoclavicular, 10 — femoral, 11 — cubital.
The ratio of small-cell LC to non-small-cell LC in the I group was 5:1, while in the II group - 1:2. The distribution of adenocarcinoma, planocellular carcinoma and large-cell carcinoma in the principal and control group was 18:1:0 and 4:3:1 respectively ($\chi^2=16.41, p<0.001$). But for the large-cell carcinoma, there were no cases of apical Pancoast — Tobias LC, diagnosed in 4.2% of other patients. According to the multivariate dispersion of Wilcoxon — Rao, RLA affects the integral clinical LC features significantly (WR=7.89, $p<0.001$).

In the principal group of RLA patients, the ratio of polyarthritis and oligoarthitis was 2:1, while in the control group - 3:1 ($\chi^2=25.15, p<0.001$). The RLA patients had no maxillary joint disorders ($\chi^2=5.57, p=0.018$), suffered from interphalangeal joint arthritis 2.3 times less frequently ($\chi^2=26.66, p<0.001$), from metacarpophalangeal joint arthritis - 2.4 times less frequently ($\chi^2=37.18, p<0.001$), radiocarpal joint arthritis — 1.8 times less frequently ($\chi^2=15.95, p<0.001$), glenohumeral joint arthritis — 4.8 times less frequently ($\chi^2=11.56, p=0.001$), all of these data reflected in Fig. 1. The symmetrical joint disorders were observed 13.0 times less frequently in the principal group, and 25.0 times more often in the control group ($\chi^2=113.65, p<0.001$).

In the non-RLA patient group, there were no enthesopathies, which afflicted 22% of patients in the principal group ($\chi^2=49.36, p<0.001$). Furthermore, the RLA patients had 7.9 times as many tendovaginitides ($\chi^2=23.18, p<0.001$), though 3.7 times as few Marie — Bamberger osteoarthropathies ($\chi^2=7.46, p=0.006$). By contrast to the RA patients (second control group), RLA was characterized by 15.7 times more frequent seronegativity by the rheumatoid factor ($\chi^2=62.77, p<0.001$), 1.5 times by the anti–citrullinated protein antibodies ($\chi^2=11.22, p=0.001$), and twice as many cases of tendovaginitides ($\chi^2=6.00, p=0.014$). If the osteousuras, intra-articular chondromic bodies, Steidi and Goff bodies were found in 51%, 24%, 6% and 4% of control patients, respectively, such X-ray-sonographic signs of LC-associated articular syndrome were absent. In the RLA group, the DAS level was 24% lower ($t=5.65, p=0.001$), while the Lansbury index was 28% lower ($t=3.57, p=0.001$).

It should be stressed that in the RLA group not only the character of articular syndrome were different, but the tumor process differed as well. In the principal (RLA) group (Fig. 2) exudative pleurisy was diagnosed twice as often ($\chi^2=5.14, p=0.02$), esophageal invasion — 14.6 times as often ($\chi^2=10.62, p=0.001$), metastatic spreading to the skeleton — 3.1 times as often ($\chi^2=42.86, p<0.001$), though these patients had no cases of neoplasms germinating into trachea ($\chi^2=4.32, p=0.04$).

The principal group did not differ from the control group of LC patients did not differ in terms of tumor stages; however, the neoplasms in the RLA group was less differentiated ($t=4.03, p<0.001$) and had a significantly more aggravated (by 14%) course ($t=3.21, p=0.002$). The number of skeletal metastases in case of RLA was 2.8 times larger ($t=5.17, p<0.001$).

**Discussion**

The RLA present in LC patients had a significant influence on the integral character of skeletal metastasizing, demonstrated by the multivariate dispersion of Wilcoxon — Rao ($WR=9.04, p<0.001$). This fact is confirmed by the performed Wilcoxon — Rao analysis ($WR=9.04, p<0.001$), by the univariate distribution and nonparametric comparative McNemar — Fisher’s test (Fig. 3). The RLA is closely associated with metastases growing into jaws ($D=23.28, p<0.001$) and pubic bone ($D=11.04, p=0.001$), absent in the control group (respectively $\chi^2=21.50, p<0.001$).

![Fig.2. Frequency of some LC signs among the principal group and control group patients (%)](image-url)
and $\chi^2=10.67$, $p=0.001$). The RLA patients had skeletal metastases significantly ($p<0.001$) more often (2.1 times) ($\chi^2=8.18$), had femoral metastases 3.5 times more often ($\chi^2=6.93$), had sacroiliac metastases 5.3 times more often ($\chi^2=148.18$), had iliac metastases 7.7 times more often ($\chi^2=42.43$), had sacral metastases 9.2 times more often ($\chi^2=41.02$).

According to the reference data, the RLA is more often observed with lung adenocarcinoma [17] and with bone metastases [18]; its course is naturally associated with C-reactive protein (CRP) and seronegativity by the rheumatoid factor (RF) [13], corresponding with the data obtained. The fact of interaction of RA and oncological pathology’s effects is mostly attributed to the manifest similarity of immune system deregulation in both diseases [19-21]. The frequency of RLA and RA’s effect interaction is aggravated by the genetic affinity to both pathological processes, namely GSAs and DEGs genes’ mutation [22, 23]. We did not observe any RLA cases resembling the adult Still’s disease or, to the same extent, isolated gonitis, pointed out by the reference data [24, 25].

**Conclusions**

1. There is a confirmed interaction of LC and co-morbid RA development; the frequency of such PNPS, clinical features of its course and association with a background tumor process (severity of neoplasm, character of growth into the adjunct organs and metastasizing, apical localization, small-cell and non-small-cell histological variant) are described.
2. RLA is characterized by the accelerated midlobar localization of tumor process, its small-cell variant, the presence of exudative pleurisy, neoplasms germinatin into esophagus and metastases growing into the skeleton.
3. There are differences of clinic-laboratory RLA and the so-called “primary” (idiopathic) RA signs.
4. RLA is characterized by oligoarthritis, enthesopathies, seronegativity by the rheumatoid factor and antibodies to cyclic citrulline peptide, low frequency of radiocarpal joint, shoulder joint, metacarpal and metatarsophalangeal joint damage, absence of osteousuras, intra-articular chondromic bodies, Steidi and Goff bodies.
5. Further LC-associated RLA studies are likely to help improve the early diagnostics quality for both groups of diseases, develop prognostic criteria and raise the effectiveness of the individual combined medical technology of treatment.

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**Information on the individual author’s contributions**

Syniachenko O.V. – study’s concept and writing the paper; Iermolaieva M.V. – analysis of the literature, design of the study; Stepko P.A. – examining the cancer patients, statistical processing; Verzilov S.M. – examining the arthritis patients, designing figures; Potapov Yu.O. - examining the patients, analysis of findings.

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Паранеопластический ревматоидоподобный артрит при раке легкого

Резюме. Актуальность. Паранеопластический синдром (ПНПС) при раке легкого (РЛ) характеризуется ревматологическими, дерматологическими, эндокринными, неврологическими и другими проявлениями. ПНПС стал актуальной проблемой современной онкологии, но особенности его течения и непосредственное течение самого опухолевого процесса остаются недостаточно изученными. Цель исследования: оценить клинико-лабораторные проявления паранеопластического (неоплазмового) ревматоидного артрита (РПА) в контексте связей с отдельными признаками РЛ. Материалы и методы. ПНПС выявлен у 258 (16%) больных РЛ, а РПА — в 41 (16%) случае ПНПС. Эти пациенты (27 мужчин и 14 женщин, средний возраст 57 лет) составили основную группу наблюдения, а остальные 217 пациентов с ПНПС (177 мужчин и 40 женщин, средний возраст 57 лет) составили основную группу наблюдения. Эти пациенты (27 мужчин и 14 женщин, средний возраст 57 лет) составили основную группу наблюдения.

Результаты. РЛ впервые диагностирована у 258 (16%) больных РЛ, а РПА — в 41 (16%) случае ПНПС. Эти пациенты (27 мужчин и 14 женщин, средний возраст 57 лет) составили основную группу наблюдения, а остальные 217 пациентов с ПНПС (177 мужчин и 40 женщин, средний возраст 57 лет) составили основную группу наблюдения.

Выводы. Формирование паранеопластического РПА наблюдается у каждого шестого больного с ПНПС, обусловленным РЛ, что сопровождается особенностями не только опухолевого процесса, но и суставного синдрома в сравнении с первичным РА. Полученные данные диктуют необходимость дальнейших исследований для выработки критериев ранней диагностики РПА.

Ключевые слова: рак; легкое; паранеопластический синдром; артрит.