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RESPIRATORY INSUFFICIENCY RELATED TO COPD ACCELERATES SYSTEMIC INFLAMMATION, UNDER-NUTRITION, AND ANGIOGENESIS IN ESOPHAGEAL MALIGNANCIES

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A number of esophageal cancer patients suffer from respiratory insufficiency due to the coexistence of chronic obstructive pulmonary disease (COPD). ***Aim:*** **To test the hypothesis that COPD-related systemic hypoxemia may result in accelerated inflammation, malnutrition, and angiogenesis in esophageal cancer patients.** ***Methods:*** **Serum levels of C-reactive protein (CRP), albumin, transferrin, interleukin-1, interleukin-6, interleukin-8, TNF-α, platelet-derived growth factor (PDGF-BB), and midkine and patient BMI and weight-loss rate were determined and compared with blood oxygenation status (pO_2, SaO_2) in 35 esophageal cancer patients and 42 controls.** ***Results:*** **The incidence of cachexia tended to be higher in patients with systemic hypoxemia (67%** ***vs*** **40%, $p = 0.169$). Mean SaO_2 level was also significantly decreased in cachectic patients (90.3** ***vs*** **93.3%, $p = 0.026$) and pO_2 exhibited a similar trend (58.0** ***vs*** **63.4 mmHg, $p = 0.120$). Transferrin (234** ***vs*** **316 mg/dl, $p = 0.005$) and albumin (31.9** ***vs*** **37.1 mg/dl, $p = 0.002$) concentrations were reduced and CRP was elevated (129.9** ***vs*** **54.7 mg/l, $p = 0.004$) in hypoxemic patients and correlated with pO_2 ($r = 0.47$, $p = 0.016$; $r = 0.48$, $p = 0.012$; $r = –0.37$, $p = 0.064$) and SaO_2 ($r = 0.52$, $p = 0.006$; $r = 0.53$, $p = 0.006$; $r = –0.40$, $p = 0.042$). Interleukin-6 (9.97** ***vs*** **2.21 pg/ml, $p = 0.005$) and midkine (2101** ***vs*** **944 pg/ml, $p < 0.001$) were elevated and PDGF-BB was decreased (12.2** ***vs*** **17.3 pg × 10^{-6}/PLT, $p = 0.014$) in hypoxemic compared with normoxemic patients. Interleukin-6 and midkine negatively correlated with pO_2 ($r = –0.44$, $p = 0.016$; $r = –0.42$, $p = 0.011$) and SaO_2 ($r = –0.54$, $p = 0.003$; $r = –0.57$, $p < 0.0001$) and PDGF-BB correlated positively ($r = 0.53$, $p = 0.003$; $r = 0.44$, $p = 0.020$). Interleukin-8 level was affected by pO_2 ($r = -0.55$, $p = 0.015$) and SaO_2 ($r = –0.55$, $p = 0.018$) only in hypoxemic patients.** ***Conclusions:*** **COPD-related systemic hypoxemia negatively affects the status of esophageal cancer patients by accelerating inflammation, under-nutrition, and angiogenesis.**

Key Words**: esophageal cancer, COPD, hypoxemia, inflammation, cytokines.**

Esophageal cancer is relatively rare, but nevertheless one of the deadliest malignancies, with five-year survival rates not exceeding 10%. Squamous cell carcinoma remains the most prevalent type, but adenocarcinomas are increasing in number, especially in the developed countries [1]. Tumor resection remains the only effective treatment option; however, it is associated with high morbidity and mortality rates [2]. In this respect, the accurate identification of high-risk patients is of great clinical importance. However, prognostication in esophageal malignancies continues to be challenging [3]. A number of models for outcome prediction, based on various epidemiological, biochemical, and clinico-pathological variables, has been developed. Preoperative systemic inflammation has frequently been recognized as an independent prognosticator of poor outcome in esophageal malignancies [2]. Recently, abnormal results of functional respiratory test have also been found to be associated with postoperative death in patients undergoing esophagectomy [4].

A considerable number of esophageal cancer patients suffers from chronic obstructive pulmonary disease (COPD), a condition defined as airflow limitation, which is not fully reversible. The pathogeneses of both COPD and esophageal cancer, of squamous origin in particular, are closely linked to tobacco smoke exposure. It is estimated that up to 90% of patients with esophageal cancers [5] and 90% of COPD patients [6] are current or former smokers. COPD is a clinically significant causative factor of the development of respiratory insufficiency in patients with esophageal malignancies. In turn, respiratory insufficiency may modify the course of cancer.

According to the current state of knowledge, both cancer [7] and COPD [8, 9] are considered systemic inflammatory diseases. The mechanisms of systemic inflammation in COPD are not fully understood. There is, however, a strong evidence for systemic oxidative stress, quantitative and functional changes in peripheral blood proinflammatory cells, and an elevation of proinflammatory cytokines [10].

The results of our previous studies showed that the coexistence of COPD-related respiratory insufficiency in patients with esophagogastric malignancies is linked with more aggressive cancer behavior. Poor systemic oxygenation status has been associated with locally advanced tumors, in which the key angiogenic factor, vascular endothelial growth factor A (VEGF-A), seems to participate [11]. COPD-related systemic hypoxemia may also stimulate the production

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Abbreviations used: APRP – acute phase-response proteins; COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; IL – interleukin; PDGF – platelet-derived growth factor; TNF – tumor necrosis factor; VEGF-A – vascular endothelial growth factor A.

of other inflammatory mediators and be responsible for nutritional changes [12]. Therefore, the present study was designed to test the hypothesis that the coexistence of COPD-related hypoxemia may result in more pronounced inflammatory response and alterations in inflammatory, nutritional, and angiogenic indices than in normoxemic patients with esophageal cancer alone.

MATERIALS AND METHODS

Patients. The study group consisted of 82 subjects: 35 esophageal cancer patients (26 with squamous cell carcinomas of the esophagus and nine with adenocarcinomas located in the lower esophagus and gastric cardia) and 47 healthy individuals (controls). The controls were blood donors (6 females and 41 males, mean age: 44.5 years), acknowledged to be healthy on the basis of routine laboratory tests, whose sera were obtained from the Regional Center of Blood Donation and Therapeutics, Wroclaw, Poland. The cancer patients (8 females and 27 males, mean age: 60 years) were clinically staged according to the guidelines of the UICC TNM [13] system on the basis of upper digestive tract (udt) endoscopy with biopsy and pathological examination, contrast radiographic studies of the udt with barium or gastrografin, posteroanterior and lateral chest radiography, ultrasound examination of the abdominal cavity and cervical nodes, thorax and abdominal cavity CT, and diagnostic laparotomy and thoracotomy. There were seven patients with stage II, 15 with stage III, and 13 with stage IV. The recruited cancer patients had long histories of heavy smoking. Analysis of blood gases was performed as part of the routine pretreatment assessment of the patients' general condition. The measurement of oxygenation status was conducted on the patients at rest breathing room air. Partial respiratory insufficiency ($pO_2 < 60$ mmHg without hypercapnia) was found in 19 of the cancer patients and was related to the co-existence of COPD. There were no differences regarding disease stage distribution (31 *vs* 42%, $p = 0.727$), the presence of regional metastasis (lymph node metastasis) (53 *vs* 81%, $p = 0.135$), or distant metastasis (25 *vs* 32%, $p = 0.723$) between the groups of cancer patients without and with systemic hypoxemia, respectively. However, there was a significantly higher incidence of locally advanced tumors (T4) in the hypoxemic than in the normoxemic patients (79 *vs* 31%, $p = 0.007$). The incidence of mild-grade anemia (n = 19) was similar in both groups (63% *vs* 48%, $p = 0.318$). The study protocol was approved by the Medical Ethics Committee of Wroclaw Medical University, Wroclaw, Poland.

Analytical methods. All examined indices were determined in sera obtained from clotted (15 min, RT) and centrifuged (15 min, 3000 rpm) blood, whereby the time regime was strictly adhered to. High-sensitive C-reactive protein (CRP) was determined by the latex particle-enhanced immunoturbidimetric method with the CRPex-HS CRP test provided from Good Biotech Corp. (Taiwan), adjusted to the micro-manual procedure. The test is based on the agglutination of serum CRP with latex particles sensitized with the ΔFc fragment of duck anti-CRP IgY antibodies increasing sample turbidity, measured spectrophotometrically at 570 nm. Albumin levels were determined by the bromocresol green method, based on the colorimetric assessment ($\lambda = 628$ nm) of the albumin-dye complex formed at acidic pH. The reagents were supplied by Stamar (Poland). Transferrin was assessed by the enhanced immunoturbidimetric method with a transferrin assay kit provided by Stamar (Poland) according to the supplier's protocol adjusted to micro-assay conditions. The test is based on enhanced reaction between serum transferrin and rabbit anti-human transferrin antibodies causing increased turbidity, measured spectrophotometrically at 595 nm. The levels of IL-1, IL-6, IL-8, and TNF-α were determined with PeliKine Compact human cytokine ELISA kits supplied by Sanquin (Holland) according to the manufacturer's instructions. Midkine concentrations were measured with a previously described double-antibody sandwich indirect ELISA (DASI-ELISA) in which rabbit (Gentaur, Belgium) and goat (RnD Systems, USA) anti-human midkine polyclonal antibodies were employed [14]. PDGF levels (PDGF-BB) were assessed with Human PDGF-BB, Stratikine ELISA from Strathmann Biotec GmbH (Germany). Due to the strong relation between serum PDGF level and platelet count (PLT), we divided each individual PDGF concentration by the subject's PLT (the corrected PDGF factor — cPDGF [pg x 10^{-6}/PLT]).

Statistical analysis. The D'Agostino-Pearson test for normality was applied for data distribution analysis. Normally distributed data (CRP, transferrin, albumin) are presented as arithmetic means, data distributed normally after log-transformation (IL-6, IL-8, midkine, and cPDGF) as geometric means, and the other values (IL-1 and TNF-α) as medians, all accompanied by 95% *CI*. The significance of differences between groups was examined with the *t*-test for independent samples or the Mann — Whitney *U* test with respect to data distribution. Correlation analysis was conducted with Spearman's or Pearson's test with respect to the data type and distribution. Differences in incidence rates were analyzed with Fisher's exact test. All tests were two-sided and *p* values $\leqslant 0.05$ were considered significant. Statistical analysis was conducted with MedCalc® version 9.2.1.0 statistical software.

RESULTS

Relationship between COPD-related chronic respiratory insufficiency and the nutritional status of esophageal cancer patients. The nutritional status of cancer patients was evaluated in terms of BMI and substantial involuntary weight loss ($\geqslant 5\%$ in a three-month period). There was no difference ($p = 0.444$) in the incidence of underweight subjects among normoxemic and hypoxemic cancer patients. There was, however, a clear tendency towards diminished pO_2 levels (56.1 mmHg (95% *CI*: 50.2–62.7) *vs* 62.2 mmHg (58.1–66.5), $p = 0.109$) and reduced saturation (90.2% (86.4–93.9) *vs*

92.3% (91.0–93.6), $p = 0.152$) in underweight cancer patients compared with those with correct weight.

Forty percent of normoxemic but 67% of hypoxemic cancer patients suffered from substantial weight loss, but the difference did not reach statistical significance ($p = 0.169$). Similarly, there was a trend towards reduced pO_2 in the cancer patients experiencing weight loss compared with those whose weight remained unaltered (58.0 mmHg (53.3–63.1) *vs* 63.4 mmHg (58.5–68.9), $p = 0.120$). This trend reached statistical significance when SaO_2 instead of pO_2 was analyzed (90.3% (88.2–92.4) and 93.3% (91.8–94.7), respectively, $p = 0.026$).

Relationship between COPD-related chronic respiratory insufficiency and acute-phase response proteins (APRP) in esophageal cancer patients. The levels of transferrin and albumin were significantly reduced in cancer patients with COPD-related chronic respiratory insufficiency (Table 1) and positively correlated with pO_2 and SaO_2 levels (Table 2). In turn, the levels of CRP were significantly elevated in cancer patients with respiratory insufficiency (see Table 1) and negatively correlated with pO_2 and SaO_2 levels (see Table 2).

Relationship between COPD-related chronic respiratory insufficiency and circulating proinflammatory and proangiogenic cytokines. The levels of circulating IL-6 and midkine were elevated in cancer patients with respiratory insufficiency, the concentrations of IL-8 and TNF-α did not differ, while cPDGF was significantly decreased and IL-1 exhibited a similar tendency (see Table 1).

IL-6 and midkine negatively correlated with pO_2 and SaO_2, while cPDGF and IL-1 either correlated positively or exhibited such a tendency. No correlation between the indices of systemic oxygenation status and the levels of circulating IL-8 and TNF-α was found (see Table 2). However, in the subgroup of cancer patients with chronic respiratory insufficiency, significant negative correlations between IL-8 and pO_2 ($r = -0.55$, $p = 0.015$) as well as SaO_2 ($r = -0.55$, $p = 0.018$) were demonstrated. There was also a tendency towards a positive relationship between IL-1 and SaO_2 ($r = 0.46$, $p = 0.088$).

Relationship between the extent of the primary tumor (disease T stage), acute-phase proteins, and proinflammatory and proangiogenic cytokines. There was a direct correlation between pO_2 ($r = -0.49$, $p = 0.004$) or SaO_2 ($r = -0.50$, $p = 0.005$) levels and tumor T stage in the esophageal cancer patients. Circulating CRP, IL-6, and midkine concentrations increased along with increasing tumor extent, while the levels of albumin and transferrin tended to decrease. The extent of the primary tumor had no impact on IL-1, IL-8, TNF-α, or cPDGF levels in the examined cohort of esophageal cancer patients (Table 3).

Table 2. The relationship between the indices of oxygenation status and serum levels of acute phase proteins, proinflammatory and proangiogenic cytokines in esophageal cancer patients

	Correlation with indices of oxygen status	
	pO_2	SaO_2
CRP	$r = -0.37$, $p = 0.064$	$r = -0.40$, $p = 0.042$*
Albumin	$r = 0.48$, $p = 0.012$*	$r = 0.53$, $p = 0.006$*
Transferrin	$r = 0.47$, $p = 0.016$*	$r = 0.52$, $p = 0.006$
IL-1	$r = 0.27$, $p = 0.145$	$r = 0.34$, $p = 0.078$
IL-6	$r = -0.44$, $p = 0.016$*	$r = -0.54$, $p = 0.003$*
IL-8	$r = -0.02$, $p = 0.924$	$r = -0.24$, $p = 0.179$
TNF-α	$r = -0.04$, $p = 0.828$	$r = -0.02$, $p = 0.905$
Midkine	$r = -0.42$, $p = 0.011$*	$r = -0.57$, $p < 0.001$*
cPDGF	$r = 0.53$, $p = 0.003$*	$r = 0.44$, $p = 0.020$*

*Statistically significant.

Table 3. The relationship between the extent of primary tumor (disease T stage) and serum levels of acute phase proteins and proinflammatory and proangiogenic cytokines in esophageal cancer patients

	Correlation with tumor T stage
CRP	$r = 0.67$, $p < 0.001$*
Albumin	$r = -0.33$, $p = 0.099$
Transferrin	$r = -0.37$, $p = 0.066$
IL-1	$r = 0.14$, $p = 0.468$
IL-6	$r = 0.75$, $p < 0.001$*
IL-8	$r = 0.26$, $p = 0.139$
TNF-α	$r = -0.03$, $p = 0.863$
Midkine	$r = 0.45$, $p = 0.008$*
cPDGF	$r = -0.19$, $p = 0.322$

*Statistically significant.

Relationship between IL-6 levels and other variables. Acute-phase proteins highly correlated with IL-6 levels. There was a substantial correlation with IL-8 and a moderate correlation with midkine (Table 4).

Table 4. The relationship between circulating IL-6 and serum levels of acute phase proteins and proinflammatory and proangiogenic cytokines in esophageal cancer patients

	Correlation with circulating IL-6
CRP	$r = 0.73$, $p < 0.0001$*
Albumin	$r = -0.60$, $p = 0.001$*
Transferrin	$r = -0.77$, $p < 0.0001$*
IL-1	$r = -0.02$, $p = 0.901$
IL-8	$r = 0.56$, $p = 0.002$*
TNF-α	$r = -0.02$, $p = 0.932$
Midkine	$r = 0.38$, $p = 0.042$*
cPDGF	$r = -0.03$, $p = 0.894$

*Statistically significant.

Relationship between COPD-related chronic respiratory insufficiency and circulating proinflammatory cells. There was a significant increase in the number of circulating white blood cells in the cancer patients with systemic hypoxemia, an effect of the elevation of neutrophils, but not lymphocytes. The

Table 1. Alterations in the concentrations of acute-phase proteins and proinflammatory and proangiogenic cytokines in esophageal cancer patients with respect to their oxygenation status

	Healthy controls (C)	Esophageal cancer patients		*p* values for pair-wise comparisons		
		Normoxemic (N)	Hypoxemic (H)	C *vs* N	C *vs* H	N *vs* H
CRP [mg/l]	6.8 (0.6–13.1)	54.7 (14.7–95.0)	129.9 (97.3–162.5)	0.024*	< 0.0001*	0.004*
Albumin [g/l]	39.4 (36.7–42.0)	37.1 (34.9–39.2)	31.9 (29.4–34.4)	0.173	0.0001*	0.002*
Transferrin [mg/dl]	293 (276–309)	316 (291–342)	234 (184–284)	0.104	0.028*	0.005*
IL-1 [pg/ml]	0.79 (0–2.10)	3.18 (1.96–4.73)	2.58 (1.63–3.87)	0.002*	0.006*	0.254
IL-6 [pg/ml]	0.70 (0.56–0.87)	2.21 (1.13–4.33)	9.97 (4.58–21.74)	0.003*	< 0.0001*	0.005*
IL-8 [pg/ml]	9.68 (7.99–11.74)	33.7 (19.5–58.5)	32.8 (19.6–54.9)	< 0.001*	0.0001*	0.936
TNF-α [pg/ml]	0.66 (0.33–1.59)	0.89 (0–3.91)	1.02 (0.44–1.99)	0.449	0.275	0.913
Midkine [pg/ml]	25 (10–63)	944 (669–1331)	2101 (1542–2861)	< 0.0001*	< 0.0001*	< 0.001*
cPDGF pgx10-6/PLT	22.5 (19.2–26.3)	17.3 (14.0–21.3)	12.2 (10.0–14.8)	0.055	< 0.0001*	0.014*

*Statistically significant.

increase in platelet count was not found to be significant (Table 5). A significant correlation was observed only between leukocyte count and both pO_2 ($r = -0.35$, $p = 0.042$) and SaO_2 ($r = -0.40$, $p = 0.020$).

Table 5. Alterations in the counts of proinflammatory cells in esophageal cancer patients in response to systemic hypoxemia

	Esophageal cancer patients		*p* value
	Normoxemic	Hypoxemic	
Leukocyte count [$\times 10^3$/μl]	8.37 (6.85–9.90)	11.77 (9.80–13.74)	0.009*
Neutrophil count [$\times 10^3$/μl]	6.09 (4.52–7.65)	9.10 (6.92–11.28)	0.025*
Lymphocyte count [$\times 10^3$/μl]	1.70 (1.25–2.15)	1.81 (1.45–2.16)	0.700
Platelet count [$\times 10^3$/μl]	292 (214–370)	322 (279–365)	0.480

*Statistically significant.

Of all the studied indices, the acute-phase proteins albumin ($r = -0.42$, $p = 0.032$), transferrin ($r = -0.41$, $p = 0.037$) and CRP ($r = 0.73$, $p < 0.0001$) as well as IL-6 ($r = 0.60$, $p < 0.001$) and midkine ($r = 0.36$, $p = 0.033$) correlated with leukocyte count. Similarly, only albumin ($r = -0.46$, $p = 0.027$), transferrin ($r = -0.46$, $p = 0.026$), CRP ($r = 0.75$, $p < 0.0001$), and IL-6 ($r = 0.67$, $p < 0.001$) correlated with neutrophil count. No significant correlation with lymphocyte count was observed, while only CRP ($r = 0.44$, $p = 0.026$) and midkine ($r = 0.38$, $p = 0.023$) correlated with platelet count and IL-6 tended to exhibit a similar trend ($r = 0.35$, $p = 0.065$).

DISCUSSION

Progressive worsening of a patient's nutritional status and loss of body weight leading to the development of cachexia is a common consequence of esophageal cancer [15] and COPD [6, 10]. Unintended weight loss is observed in about 50% of COPD patients with chronic respiratory failure [10] and in about 80% of newly diagnosed esophageal cancer patients [16]. Tissue hypoxia, an effect of systemic hypoxemia, has been implicated in increasing the metabolic rate [10]. We therefore investigated, whether the presence of COPD-related respiratory insufficiency was associated with a higher prevalence of under-nutrition in patients with esophageal malignancies. However, we failed to demonstrate such an association in the current cohort of patients. BMI has been criticized as an inadequate index of cancer cachexia since it excludes those cancer patients who exhibit normal BMI although they experience substantial weight loss [15, 17]. Accordingly, the measurement of oxygenation status revealed a clear tendency towards decreased oxygen partial pressure and saturation in cancer patients with COPD-related respiratory insufficiency. The presence of accelerated and involuntary weight loss is considered a stronger indicator of cancer cachexia [18]. Indeed, the differences obtained with this index were more significant. The lack of statistical significance may result from the relatively low number of analyzed cases, inadequate to demonstrate differences in the incidence of weight loss. The prevalence of weight loss in esophagogastric cancer is high, reaching 80% of newly diagnosed cases [18]. On the other hand, esophageal cancer is rare [1] and COPD affects only 10% of smokers [6], resulting in a limited number of patients available for the current study.

Supporting the thesis of a worsening of nutritional status of cancer patients by systemic hypoxemia, we found a significant decrease in the levels of nutritional markers, transferrin and albumin, in patients with COPD-related respiratory insufficiency. Moreover, the concentrations of both markers positively correlated with pO_2 and SaO_2 levels. The association between systemic hypoxemia and cachexia was further supported by the elevation in IL-6 levels, a procachectic cytokine found to be elevated in esophagogastric cancer patients with substantial weight loss [17], and its negative correlation with pO_2 and SaO_2. There was no difference in the levels of the other two key procachectic cytokines TNF-α and IL-1. However, their up-regulation seems to be time limited and to have only a local range, while systemic elevation has been rarely detected [19].

Tumor tissue hypoxia has been linked with amplified aggressiveness of neoplasms [20], but the effect of systemic hypoxemia has not been extensively studied. We previously linked systemic hypoxemia with a higher extent of primary tumor and elevated angiogenic potential, manifested by a significant increase in circulating VEGF-A [11]. The negative impact on nutritional status reported in the present study further contributes to the adverse effects of systemic hypoxemia in esophageal cancer patients.

In addition to the previously reported VEGF-A elevation [11], here we revealed a systemic hypoxemia-related increase in the concentration of midkine, another mediator of angiogenesis [21]. We also confirmed midkine's relationship to disease T stage, as demonstrated earlier [22]. Midkine's elevation in response to hypoxia thus provides further evidence for the existence of a link between systemic hypoxemia and greater cancer aggressiveness, mediated by angiogenic factors. Similarly to VEGF-A [20], midkine has previously been shown to be up-regulated by hypoxia-inducible factor 1α (HIF-1α) [23], a key redox-sensitive transcription factor [20]. Moreover, the binding sites for nuclear factor κB (NFκB) and activator protein-1 (AP-1), other oxygen-dependent transcription factors [20], have been demonstrated in the midkine promoter sequence as well [24]. However, midkine oversecretion in response to systemic hypoxemia has not been reported so far. Midkine elevation may reflect the ongoing process of repair and restructuring of the airways in the course of COPD [25], since midkine's involvement in lung remodeling has been previously reported [23]. Interestingly, we showed IL-8 elevation in response to a tumor-bearing state, but no further rise in hypoxemic patients, although a gene of this proinflammatory and proangiogenic cytokine is transactivated by NFκB [20]. Nevertheless, IL-8 level increased along with worsening of patients' oxygenation status, but the impact of systemic hypoxemia was demonstrated exclusively in patients with respiratory insufficiency.

Surprisingly, some pro-angiogenic cytokines appear to be inversely regulated. We observed a decrease in cPDGF-BB levels in cancer patients with

COPD-related respiratory insufficiency, despite the fact that PDGF gene has both a hypoxia-responsive element (HRE) sequence as well as a binding site for AP-1 [20]. Moreover, PDGF has been implicated in the remodeling of the airway wall in the course of COPD [26]. We have no explanation for this phenomenon, but it seems to indeed be related to the factor's diminished secretion, since platelet count was not significantly altered. Moreover, despite the lack of differences in mean levels, IL-1 also appears to be negatively affected by the decrease in blood oxygenation.

The depletion of albumin and transferrin levels may contribute to enhanced oxidative stress and inflammatory response in cancer patients with COPD. Correspondingly, we demonstrated an elevation in CRP, inversely correlating with systemic oxygenation status. CRP elevation has been found to be an independent prognostic factor in esophageal cancer [2]. Up-regulation of CRP secretion has also been demonstrated in COPD, being more pronounced during disease exacerbation [10]. Our study shows further CRP elevation in cancer patients with coexisting respiratory insufficiency related to COPD. However, the impact of systemic hypoxemia on CRP concentration, similarly to transferrin and albumin, might be mediated by IL-6, a well-known modulator of the acute-phase response [27]. Indeed, the levels of acute-phase proteins more strongly correlated with IL-6 than with pO_2 and SaO_2 levels. Interestingly, CRP elevation markedly reflected the increase in the extent of primary tumor, suggesting that tumor cells might participate in CRP secretion. This is in agreement with the results of immunohistochemical studies by Nozoe et al. [28] demonstrating CRP expression in esophageal squamous cell carcinoma cancer tissues.

In line with CRP elevation, we also observed a significant increase in leukocyte and neutrophil counts, moderately related to pO_2 and SaO_2 levels. This observation is consistent with the current knowledge on the involvement of peripheral neutrophils in the systemic effects of COPD [10]. A substantial increase in the number of inflammatory cells as well as enhanced cell activation have been linked to the presence of elevated levels of circulating chemoattractants [29]. Midkine, demonstrated here to be oversecreted in cancer patients with systemic COPD-related hypoxemia, is a potent neutrophil and macrophage chemoattractant [30]. Correspondingly, midkine levels correlated with white blood cell counts in the examined cohort of cancer patients.

We hypothesized that COPD-related respiratory insufficiency in patients with esophageal malignancies may be associated with more pronounced inflammation, under-nutrition, and angiogenesis. Generally, our results seem to confirm this hypothesis. Taking into account the impact these factors have on prognosis, we believe that our results may contribute not only to a better understanding of the effect systemic hypoxemia exerts on the course of cancer disease, but may help in better management of esophageal cancer patients as well.

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COPD-ЗАВИСИМАЯ РЕСПИРАТОРНАЯ НЕДОСТАТОЧНОСТЬ УСИЛИВАЕТ СИСТЕМНОЕ ВОСПАЛЕНИЕ, ИСТОЩЕНИЕ И АНГИОГЕНЕЗ ПРИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЯХ ПИЩЕВОДА

Многие больные раком пищевода страдают от респираторной недостаточности из-за развития хронического обструктивного легочного заболевания (COPD). *Цель:* Проверить гипотезу о возможной связи системной гипоксемии, ассоциированной с COPD, с усилением воспалительных процессов, истощением и ангиогенезом у больных раком пищевода. *Методы:* у 35 больных раком пищевода и 42 здоровых доноров определяли уровень CRP, альбумина, трансферина, интерлейкина-1, интерлейкина-6, интерлейкина-8, TNF-α, PDGF-BB и мидкина в сыворотке крови, показатели BMI и потери веса больных, а также показатели уровня оксигенации крови (pO_2, SaO_2). *Результаты:* частота возникновения кахексии была выше у больных с системной гипоксемией (67 против 40%, $p = 0{,}169$). Средний уровень SaO_2 был также значительно снижен у больных с кахексией (90,3 против 93,3%, $p = 0{,}026$), с той же тенденцией и для уровня pO_2 (58,0 против 63,4 mmHg, $p = 0{,}120$). Концентрации трансферина (234 против 316 мг/дл, $p = 0{,}005$) и альбумина (31,9 против 37,1 мг/дл, $p = 0{,}002$) были снижены, CRP повышен (129,9 против 54,7 мг/л, $p = 0{,}004$) у гипоксемических пациентов, что кореллировало с показателями pO_2 ($r = 0{,}47$, $p = 0{,}016$; $r = 0{,}48$, $p = 0{,}012$; $r = -0{,}37$, $p = 0{,}064$) и SaO_2 ($r = 0{,}52$, $p = 0{,}006$; $r = 0{,}53$, $p = 0{,}006$; $r = -0{,}40$, $p = 0{,}042$). Уровень интерлейкина-6 (9,97 против 2,21 pg/ml, $p = 0{,}005$) и мидкина (2101 против 944 pg/ml, $p < 0{,}001$) был также повышен, а уровень PDGF-BB понижен (12,2 против 17,3 pg × 10^{-6}/PLT, $p = 0{,}014$) у гипоксемических больных по сравнению с показателями при нормоксемии. Уровни интерлейкина-6 и мидкина негативно кореллировали с показателями pO_2 ($r = -0{,}44$, $p = 0{,}016$; $r = -0{,}42$, $p = 0{,}011$) и SaO_2 ($r = -0{,}54$, $p = 0{,}003$; $r = -0{,}57$, $p < 0{,}0001$) и позитивно — с PDGF-BB ($r = 0{,}53$, $p = 0{,}003$; $r = 0{,}44$, $p = 0{,}020$). На уровень интерлейкина-8 влияли pO_2 ($r = -0{,}55$, $p = 0{,}015$) и SaO_2 ($r = -0{,}55$, $p = 0{,}018$) только у больных с гипоксемией. *Выводы:* ассоциированная с COPD системная гипоксемия негативно влияет на состояние больных раком пищевода за счет ускорения воспалительных процессов, истощения и ангиогенеза.

Ключевые слова: **рак пищевода, COPD, гипоксемия, воспаление, цитокины.**