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Original Article / Özgün Makale

Bronchial cytokine level changes in lung cancer operations

Akciğer kanser ameliyatlarında bronşiyal sitokin düzeylerindeki değişiklikler

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Background: This study aims to evaluate effects of lung resection type, lymphovascular invasion and type of cancer on bronchial cytokine levels [interleukin (IL)-6, IL-8 and tumor necrosis factor-alpha (TNF-α)].

Methods: Twenty-eight patients (27 males, 1 female; mean age 65.9±7.6 years; range 48 to 79 years) with lung cancer undergoing lung resection between August 2010 and December 2011 were enrolled in the study. None had fever, empyema or signs of lower respiratory tract infection. Bronchial lavage samples were collected from both sides of main bronchial systems right before the operation and from the operated bronchus right after the operation.

Results: No significant difference was observed between preoperative bronchial cytokines of both bronchial sites (with and without tumor). Tumor-side bronchial IL-6 and TNF-α were significantly increased after the operation compared to preoperative levels (p=0.001, p=0.045). Compared to lobectomy, IL-6 levels of the patients who underwent pneumonectomy were significantly higher (p=0.004). Significant difference was observed between preoperative contralateral bronchial IL-8 levels of patients in whom decortication was performed as an additional operational procedure and those underwent an isolated lung resection (p=0.017). There was a positive correlation between stage, stage subgroup, and preoperative contralateral bronchial IL-6 levels (p=0.005, p=0.027). Postoperative IL-6 levels were found to be higher in patients with lymphovascular invasion (p=0.008).

Conclusion: Bronchial cytokines, IL-6 and TNF-α levels, were markers of surgical injury on the tumor side from bronchial system following operation. As the tumor stage increases, the entire lungs are affected and the inflammatory response is expanded to contralateral hemithorax. Postoperative IL-6 levels may be an indicator of lymphovascular invasion. The extensiveness of the operation also affects the inflammatory response; IL-6 levels of the patients undergoing pneumonectomy may have significantly higher than lobectomy. Thus, it shows a relationship between IL-6 synthesis and the degree of surgical injury.

Keywords: Bronchial cytokines; lung cancer; lymphovascular invasion; resection.

Amaç: Bu çalışmada akciğer rezeksiyon tipinin, lenfovasküler invazyonun ve kanser türünün bronşiyal sitokin düzeyleri üzerine [interlökin (IL)-6, IL-8 ve tümör nekroz faktör-alfa (TNF-α)] etkileri değerlendirildi.

Çalışma planı: Ağustos 2010 - Aralık 2011 tarihleri arasında akciğer kanseri nedeniyle akciğer rezeksiyonu uygulanan 28 hasta (27 erkek, 1 kadın; ort yaş 65.9±7.6 yıl; dağılım 48-79 yıl) çalışmaya alındı. Hiçbirinde ateş, ampiyem veya alt solunum yolu enfeksiyonu bulguları yoktu. Bronş lavajı örnekleri hemen ameliyat öncesi ana bronş sistemlerinin her iki tarafından ve hemen ameliyat sonrası ameliyat edilen ana bronştan toplandı.

Bulgular: Ameliyat öncesi her iki bronşiyal bölgeden alınan bronş sitokinleri arasında (tümörü olan ve olmayan) anlamlı farklılık gözlenmedi. Tümör tarafı bronşiyal IL-6 ve TNF-α düzeyleri ameliyat öncesi düzeyler (p=0.001, p=0.045) ile karşılaştırıldığında, ameliyat sonrası anlamlı ölçüde artmıştı. Pnömonektomi uygulanan hastalarda IL-6 düzeyleri lobektomiye kıyasla yüksek bulundu (p=0.004). İlave bir cerrahi işlem olarak dekortikasyon yapılan hastalar ile izole sadece akciğer rezeksiyonu uygulanan hastaların ameliyat öncesi kontralateral bronşiyal IL-8 düzeyleri arasında anlamlı farklılık gözlendi (p=0.017). Evre, evre alt grubu ile ameliyat öncesi kontralateral bronşiyal IL-6 düzeyi (p=0.005, p=0.027) arasında pozitif ilişki vardı. Ameliyat sonrası IL-6 düzeyleri lenfovasküler invazyon saptanan (p=0.008) hastalarda daha yüksek bulundu.

Sonuç: Ameliyat sonrası bronşiyal sistem tümör tarafı bronşiyal sitokin IL-6 ve TNF-α düzeyleri cerrahi travmanın bir göstergesi olabilir. Tümör evresi arttıkça, tüm akciğer etkilenir ve enflamatuvar yanıt kontralateral hemitoraksa kadar yayılır. Ameliyat sonrası IL-6 düzeyleri lenfovasküler invazyonun bir göstergesi olabilir. Ameliyatın büyüklüğüne göre enflamatuvar yanıt etkilenmektedir; pnömonektomi uygulanan hastaların IL-6 düzeyleri lobektomilere kıyasla anlamlı düzeyde yüksek seyredebilir. Bu sonuç, IL-6 sentezi ve cerrahi travma derecesi arasındaki ilişkiyi göstermektedir.

Anahtar sözcükler: Bronşiyal sitokinler; akciğer kanseri; lenfovasküler invazyon; rezeksiyon.

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Cytokines mediate numerous physiological and immune reactions which are manifested in various biological effects, including tumoricidal activity. Furthermore, an inflammatory response has been observed in both local and systemic lung cancer.[1]

Tumor necrosis factor-alpha (TNF-α) is a pleiotropic cytokine that can be either constitutively produced or induced in human tumors.[2] It has emerged as one of the many mediators, which either alone or in combination, appear to mediate both antiproliferative and tumorigenic effects in malignant tumors. Interleukin 6 (IL-6) and IL-8 are produced and expressed by a variety of cells, including tumor cell lines.[2-4] Interleukin 8 is an important cytokine that is involved in proinflammatory and reparative processes,[5] and it is widely expressed in tumoral, stromal, and endothelial cells.[6,7] Interleukin 6 is a proinflammatory cytokine released in response to infection, trauma, and neoplasia, and it plays a key role in the immune and acute-phase responses as well as hematopoesis.[8]

Thoracotomies are one of the most invasive surgical procedures. Thoracic surgery, such as a lobectomy, triggers a more severe systemic inflammatory reaction than intraabdominal surgery,[9] and inflammatory cytokines act as reliable markers of surgical stress associated with this type of operation.

Bronchial lavage is an important tool for assessing the inflammatory state in the alveolar compartment of the lungs since it can be used to monitor changes in the immune system by measuring the cytokines or the inflammatory mediator concentrations.[10]

The aim of this study was to evaluate the effects of different types of lung resection, lymphovascular invasion, and forms of cancer on bronchial cytokine levels (IL-6, IL-8, and TNF-α).

PATIENTS AND METHODS

The bronchial lavage samples of 28 lung cancer patients (27 males, 1 female; mean age 65.9±7.6 years; range 48-79 years) who had undergone surgery were collected between August 2010 and December 2011 at Adnan Menderes University Hospital, Department of Thoracic Surgery. Local ethics committee approval was obtained, and all of the patients gave their written informed consent to participate in the study. Patients with immune deficiency and those who had used corticosteroids were excluded from the study. None of the participants had fever, empyema, or signs of lower respiratory tract infection. All of the patients underwent a bronchoscopy, and 20 were evaluated via positron emission tomography-computed tomography (PET-CT). In addition, three underwent a mediastinoscopy as part of their preoperative work-up.

All of the patients also underwent double lumen intubation and a posterolateral thoracotomy. Bronchial lavage, which is not the same as bronchoalveolar lavage (BAL), was performed in the operation room from both sides of the main bronchial systems right before the operation and from the operated bronchus immediately afterwards (before extubation) via catheter lavages using 20 ml aliquots of normal saline after isolating the main bronchial systems from each other by double lumen intubation. This was especially important for those who had undergone a pneumonectomy. The aliquots were then pooled and centrifuged at 200 g for 10 minutes, and the supernatants were frozen at -80 ˚C. Next, the concentrations of IL-6, IL-8, and TNF-α in BAL were measured using the eBioscience Platinum enzyme-linked immunosorbent assay (ELISA) kit (eBioscience, Vienna, Austria) according to the manufacturer's instructions.

The patients' demographic data (i.e., age, gender, tumor type, lymphovascular invasion stage, operation time, operation procedure and perioperative findings) was then recorded, and those whose pathological diagnosis was not squamous cell carcinoma (SCC) or adenocarcinoma were not included in this study.

Lymphovascular invasion was reported when tumor cells were seen on a histological examination within the lymphatic channels, veins or venules, and/or arteries or arterioles. The presence of tumor emboli within peritumoral, endothelial-lined spaces that had been stained with hematoxylin and eosin (H-E) signified a positive lymphovascular invasion.

Statistical analysis

Statistical analysis was performed with the SPSS version 16.0 for Windows software program (SPSS Inc., Chicago, Illinois, USA). The Wilcoxon signed-rank test was used to evaluate the differences between the preoperative and postoperative cytokine concentrations, and the nonparametric Wilcoxon signed-rank test for two related samples was performed to calculate the differences between the preoperative (tumor side and non-tumor side) and postoperative (tumor side) cytokine levels. In addition, the Kruskall-Wallis test was used to calculate the differences according to operation type (lung biopsy via thoracotomy, lobectomy, or pneumonectomy), and any significant differences were reanalyzed using the Mann-Whitney U test.

The differences between the subgroups of patients (i.e., chest wall involvement and pleural thickening)

Table 1. Operative data of the bronchial carcinoma patients (n=28)

	n	%
Type of lung resection		
Lung biopsy	14.3	4
Lobectomy	67.9	19
Pneumonectomy	17.9	5
Stage 1	39.3	11
A	10.7	3
B	28.6	8
Stage 2	28.6	8
A	14.3	4
B	14.3	4
Stage 3	28.6	8
A	21.4	6
B	7.1	2
Stage 4	3.6	1
Type of cancer		
Squamous cell carcinoma	64.3	18
Adenocarcinoma	35.7	10
Lymphovascular invasion		
Negative	46.4	13
Positive	53.6	15

were also analyzed with the Mann-Whitney U test, and correlations between cancer stages, cancer stage subgroups, and cytokine levels were assessed using a Spearman's rho test. A *p* value of 0.05 was considered to be statistically significant.

RESULTS

The lung cancer stages, type of lung resection, histological type of cancer, and presence of lymphovascular invasion are shown in Table 1.

A lung biopsy via a thoracotomy was performed on four patients. Esophagus invasion was found in one patient, and mediastinal invasion was detected perioperatively in another patient. Pulmonary vein invasion necessitating an intrapericardial dissection was identified in one patient, but dense adhesions in the intrapericardial area caused by previous cardiac bypass surgery were observed upon exploration, and the operation was terminated to avoid damage to the bypass grafts. The last patient had undergone a lobectomy for lung cancer four years earlier, and his pulmonary capacity was limited to the extent that another anatomical resection was not possible; hence, the operation was terminated after the wedge resection.

No significant differences were observed between the preoperative bronchial cytokine levels in either of the bronchial sides (with or without tumors). The postoperative bronchial IL-6 side (25%=15.50, 75%=90.93; median 25.87) (p=0.001) and TNF-α (25%=6.39, 75%=8.94; median 7.25) (p=0.045) were significantly increased compared with the preoperative tumor side IL-6 (25%=12.79, 75%=18.46; median=15.66) and TNF-α levels (25%=5.78, 75%=7.25; median=6.21) (Figures 1 and 2) were also higher, whereas the IL-8 levels did not seem to be affected.

The rise in IL-6 levels was affected by operation type as the levels in the cases who underwent a pneumonectomy (25%=88.11, 75%=155.30; median=146.92) were markedly higher than the lobectomy cases (25%=14.41, 75%=50.79; median=24.37) (p=0.004) (Figure 3). However, the IL-8 and TNF-α levels did not change according to resection type.

Chest wall resection because of chest wall involvement was performed on three cases. One patient underwent a pneumonectomy and the other two had lobectomies. Significant differences were observed between the preoperative IL-6 levels on the tumor side of these patients (25%=9.52, 75%=13.05; median 9.58) versus those without chest wall involvement

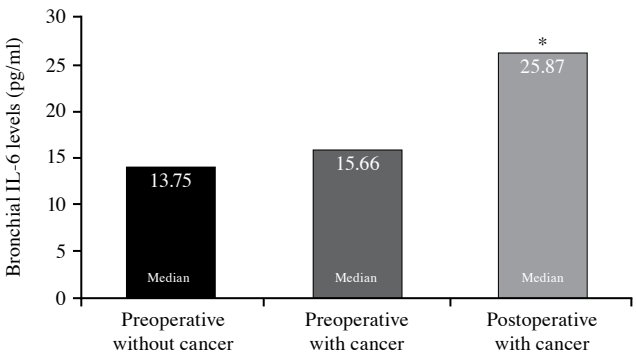

Figure 1. Comparison of preoperative and postoperative bronchial IL-6 levels. * p=0.001.

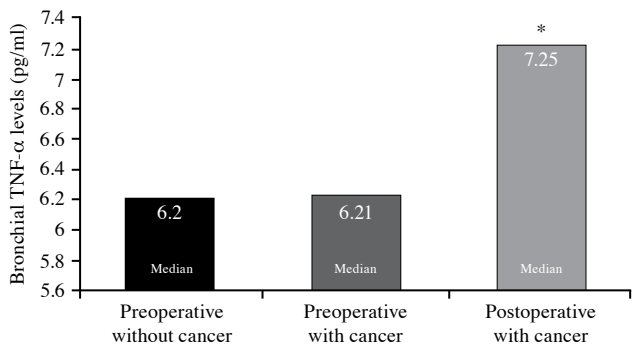

Figure 2. Comparison of preoperative and postoperative bronchial TNF-α levels. * p=0.045.

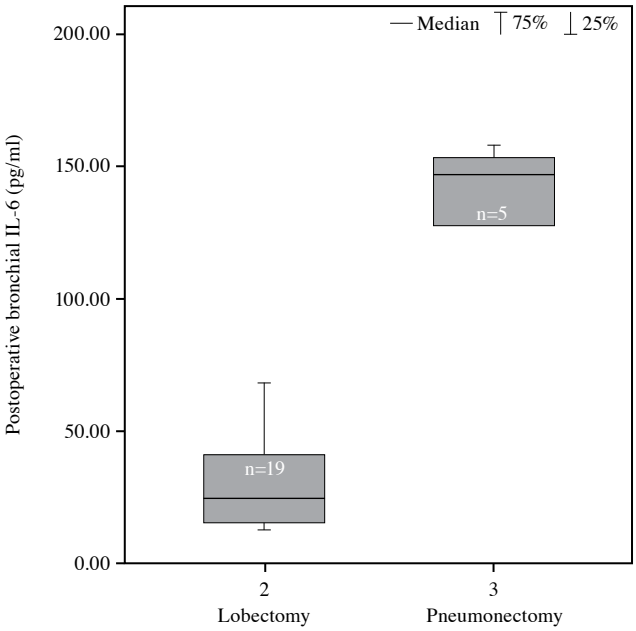

Figure 3. Comparison of the postoperative bronchial IL-6 levels in the patients who underwent a lobectomy versus a pneumonectomy (p=0.004).

(25%=12.92-75%=18.85; median 16.61) (p=0.019). Furthermore, we were not able to determine a definitive opinion on some points in a few cases in the subgroups. However, when we compared the 17 patients who underwent a lobectomy with the two who underwent this procedure due to chest wall involvement (n=2), the preoperative IL-6 levels on the tumor side differed significantly (p=0.012).

During the operation, we observed dense fibrosis of the visceral pleura, which led to fusion of the visceral and parietal membranes and reduced mobility of the lung without signs of previous empyema; therefore, total decortication was performed as an additional procedure on seven of the patients, with two undergoing a lung biopsy and five undergoing a lobectomy.

We observed significant differences in the preoperative contralateral IL-8 levels between the patients with pleural thickening (25%=2,035.81-75%=6,084.62; median 3,981.45) and those without this symptom (25%=589.40-75%=2,343.38; median 1,704.78) (p=0.017) (Figure 4). When the pleural thickening was compared with regard to operation type (lung biopsies with and without decortication and lobectomies with and without decortication), no significant differences were seen in the IL-8 and TNF-α levels. In addition, significant differences in the postoperative IL-6 levels on the tumor side were noted between the 14 patients who underwent a lobectomy and the five who had pneumonectomies (p=0.014) as well as the five patients who had a lobectomy because of pleural thickening and the pneumonectomy patients (p=0.008). However, no differences were seen between the patients who had a lobectomy and those who underwent this procedure due to pleural thickening as well as between the patients who underwent a lung biopsy and those who had this procedure due to pleural thickening. However, it should be noted that these procedures were performed on a small number of patients.

Moreover, there was a positive correlation between the cancer stages, cancer stage subgroups, and preoperative contralateral bronchial IL-6 levels (stage; r=0.520; p=0.005) (subgroups; r=0.417; p=0.027).

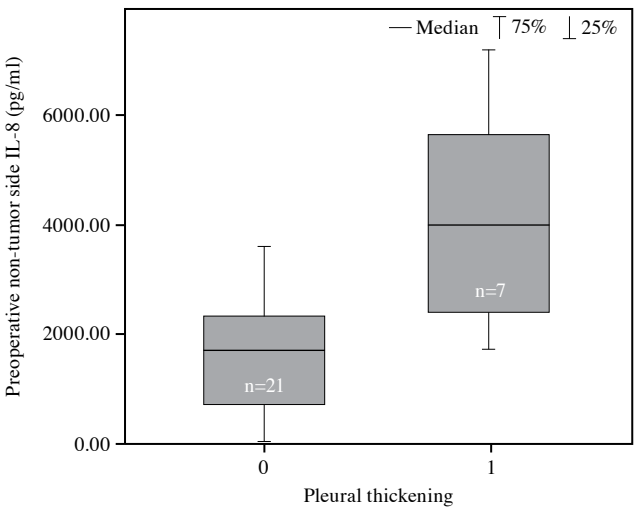

Figure 4. Comparison of preoperative non-tumor-side bronchial IL-8 levels according to pleural thickening. p=0.017.

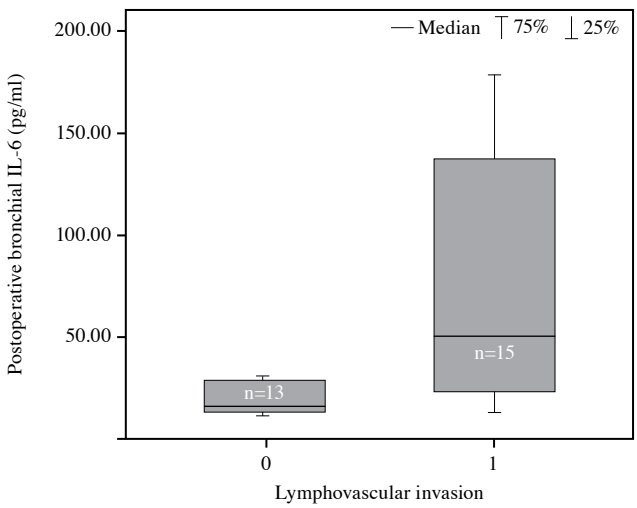

Figure 5. Pre- and postoperative cytokine levels of cases with and without lymphovascular invasion. p=0.008.

However, we found no statistically significant differences in the cytokine levels of the patients with SCC and adenocarcinoma, but the postoperative IL-6 levels were higher (p=0.008) when lymphovascular invasion was present (Figure 5).

DISCUSSION

This prospective study was designed to explore the association and examine any alterations associated with local inflammation according to the operation procedure, type of cancer, and presence of lymphovascular invasion in lung cancer patients who underwent thoracic surgery. In addition, we investigated the bronchial inflammatory process of the affected lung before and after surgery and the contralateral lung preoperatively. Numerous articles have been published regarding the effect of anesthesia type on cytokines,[11-14] but in our study, all of the patients received similar forms of anesthesia, and the operation times did not vary significantly.

The proliferation or growth of tumor cells by cytokines may be controlled either by their direct or indirect effects on angiogenesis or host immunity.[15] Tumor necrosis factor-alpha is important in the early events related to tumorigenesis, control of cytokines, chemokines, and adhesion molecules, and pro-angiogenic activities.[16] Furthermore, Arenberg et al.[11] reported that IL-8, which is known to recruit inflammatory neutrophils and promote the interaction between tumor cells and inflammatory cells, has been produced in non-small cell lung cancer (NSCLC). Additionally, Smith et al.[17] determined that IL-6 may have a pleiotropic function that involves malignant transformation and progression against tumor cells along with the promotion of an immune response by the inhibition of regulatory T cells.

In our study, the effects of cancer on cytokine changes were assessed by comparing the tumor side and contralateral bronchial cytokine levels. Katsumada et al.[18] showed that IL-6 levels were correlated with T_3, N_2, and stage IV cancer and also indicated that IL-6 might be involved in tumor growth. In another investigation by Matanić et al.[19] IL-6 and TNF-α levels were increased in lung cancer patients, but these levels progressively decreased as the clinical cancer stage progressed. Staal-van den Brekel et al.[20] also detected the presence of immunohistochemical staining patterns for TNF-α, IL-6, and IL-8 and the enhanced expression of both TNF receptors in tissue samples obtained from resection specimens of NSCLC. Moreover, Atwell et al.[21] determined that there were baseline elevations in cytokine levels in patients with malignant lung cancer who underwent thoracic surgery. We found no significant differences among the cytokine levels (IL-6, IL-8, and TNF-α) at either bronchial site preoperatively (with or without tumors), but there was a positive correlation between the cancer stage, cancer stage subgroups, and preoperative contralateral bronchial IL-6 levels. Although IL-6, IL-8, and TNF-α have systemic properties and activate T lymphocytes and macrophages, they showed no differences in the bronchial area related to malignancy. Furthermore, our data suggests that the local inflammatory response via IL-6 production revealed itself in the contralateral hemithorax according to the cancer stage.

The effects of surgery on cytokine changes can be assessed by comparing the pre- and postoperative bronchial cytokine levels. We determined that the IL-6 and TNF-α levels were increased on the bronchial system on the side where the tumor was located following the operation, whereas there were no significant changes with respect to IL-8. Franke et al.[22] and Esme et al.[23] demonstrated that there were elevated IL-6 and TNF-α levels in the blood following surgery but that there were no changes in the IL-8 levels during the perioperative period, just as we discovered in our findings. Furthermore, according to Franke et al.,[22] the IL-8 levels were selectively elevated after cardiac surgery, and the myocardium was identified as the major source of this cytokine. Additionally, Sugasawa et al.[24] identified elevated IL-8 levels in BAL specimens taken after lung surgery, which is contrary to our results. However, they also found increased levels of IL-6 and TNF-α when bronchial lavage was performed after lung surgery just as we did.

The inflammatory response is affected by more complicated surgical procedures. For example, in our study, the IL-6 levels of the patients who underwent a pneumonectomy were markedly higher than those who had a lobectomy. In our patients who underwent a pneumonectomy, the bronchial lavage samples were taken directly from the bronchial stump; thus, we observed a relationship between IL-6 synthesis and the degree of surgical trauma[22] When Craig et al.[25] compared a pulmonary lobectomy conducted via video assisted thoracic surgery (VATS) along with a conventional open thoracotomy, they found reduced activity in the acute phase of cytokine IL-6, which indicated less surgical trauma.

In our study, chest wall resection and decortication were also necessary in some of the cases. The preoperative IL-6 levels on the tumor side of the patients with chest wall involvement were significantly

lower than those without this involvement. This may be explained by the tumor itself or by the infiltrating cells that produce immunosuppressive molecules that affect the production of cytokines in the alveolar compartment. This production can be identified via bronchial lavage. However, the number of chest wall resections was limited in our study; thus, further studies are needed with a larger patient population to confirm our results. When we investigated the cytokine changes in the patients with chest wall involvement, our purpose was to bring attention to this topic in order to prompt to new research. It was not to provide definitive answers.

In our study, the contralateral preoperative bronchial IL-8 levels in the patients who underwent decortication in addition to the surgical procedure were significantly higher than the other study participants. There are two possible explanations for the increased preoperative IL-8 levels in the bronchial systems on the side without tumors. First, previous pleural inflammation that caused pleural thickening (tumor-related, post-obstructive pneumonia/pleurisy or non-tumor-related infections) can spread to the contralateral hemithorax. Even in cases in which the inflammatory agent does not exist, as in our study, the bronchial IL-8 levels can remain high. Furthermore, in a study by Chung et al.[26] the pleural IL-8 levels of complicated parapneumonic effusions were higher than for non-complicated effusions. Another explanation for the elevated IL-8 levels is that that the inflammatory agent might cause systemic inflammation and increased levels of IL-8 in the blood as it passes into the contralateral bronchial system. In fact, this can occur even without the presence of this agent. However, we did not evaluate the blood cytokine levels in this study; therefore, this topic needs to be clarified via other studies that feature a larger sample size.

Pleural thickening can be defined as a fibrous visceral and parietal pleural peel along with inflammation of the pleural cavity that may continue during the early postoperative period. It plays a central role in the pathogenesis of pleural fibrosis that leads to perioperative parenchymal lacerations. Therefore, the incidence of major postoperative complications, such as sepsis, bronchopleural fistulas, peripheral bronchoalveolar air leaks, and hemorrhage, is substantially higher in patients who require combined pulmonary resection and decortication.

In our study there were no statistically significant differences between the cytokine levels in patients with SCC and adenocarcinoma, and this contrasts with the findings of Arias-Diaz et al.[27] who determined that the increased levels of TNF-α and IL-6 in BAL with bronchogenic SCC need further investigation.

The postoperative IL-6 levels in our study were higher in the patients with lymphovascular invasion than those who did not have this condition. This possibly indicates the role of tumor infiltration in the bronchial inflammatory response, or it may reflect the increased spread of cells during the process of proliferation as well as the subsequent invasion of tumor cells.[28]

Our study had some limitations. We identified the perioperative cytokine response pattern in thoracic operations involving patients with lung malignancy, but the study group and subgroups were small. We do not know whether a larger patient population would have significantly changed the results, so we recommend that further studies be carried out to confirm our findings.

Conclusion

This study determined the pre- and postoperative local cytokine responses of lung cancer patients who underwent thoracic surgery. According to our findings, the bronchial cytokine levels of lung cancer patients who underwent lung resection were significantly altered, except for the IL-8 levels. Furthermore, the increased IL-6 and TNF-α levels were markers of surgical injury on the bronchial system on the tumor side following the operation. We also determined that the tumor stage was affected by the local inflammatory response since it expanded to the contralateral hemithorax. In addition, the increase in postoperative IL-6 levels might be an indicator of lymphovascular invasion. Moreover, more complicated surgical procedures had a greater effect on the inflammatory response as the IL-6 levels of the patients who underwent pneumonectomies were significantly higher than those who had lobectomies. Therefore, we observed a relationship between IL-6 synthesis and the degree of surgical trauma. The higher contralateral bronchial IL-8 levels might indicate the presence of pleural adhesions and thickened pleurae before the operation and the need for decortication as an additional procedure, thus forcing the surgeon to deal with the possibility of postoperative complications associated with this extra procedure. While we believe our results were significant, further studies with a larger patient population are needed to verify our findings.

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