



## Bronchial Cytokine Changes Following Bronchial Resection and Reconstruction for Carcinoid Tumor

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### Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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### ABSTRACT

As bronchial carcinoids are known to be notably rare, adequate histochemical investigations couldn't have been carried out on these types of tumors hitherto. In this study, we investigated bronchial cytokines in a carcinoid tumor localized in the left main bronchus. Bronchial resection and reconstruction was performed without the lung resection. Bronchial lavage samples were obtained from both sides of main bronchial system preoperatively and postoperatively. TNF- $\alpha$ , IL-8 and IL6 levels were measured by ELISA. Preoperative TNF- $\alpha$  and IL-8 levels were found to be 2-folds and 5-folds higher on the tumor side respectively (TNF- $\alpha$ ; 14.184 pg/ml and IL-8; 3359.86 pg/ml) compared to tumor-free bronchial system (TNF- $\alpha$ ; 6.886 pg/ml, IL-8; 615.072 pg/ml). Interestingly, both cytokine levels were found to be equal and within normal ranges on both sides subsequent to bronchial resection and reconstruction. There were no significant difference in IL-6 levels between two bronchial systems preoperatively (IL-6 levels of right bronchus, 16.44 pg/ml; levels of left bronchus, 19.11 pg/ml). However, there was more than four-fold increase in postoperative levels (IL-6 level; 89.41 pg/ml). In our study, we found that preoperative TNF- $\alpha$  and IL-8 levels were higher compared to the

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postoperative ones; whereas IL-6 levels showed a significant increase, postoperatively. These findings led us through the idea that carcinoid tumors might be activating the inflammatory process among TNF- $\alpha$  and IL-8 and the surgical bronchoplastic procedure could be the cause of enhanced IL-6 response.

**Keywords:** Bronchial resection; reconstruction; carcinoid tumor; cytokines.

## 1. INTRODUCTION

Broncho-pulmonary carcinoid tumors are low-grade malignant neuroendocrine tumors that show fairly benign behavior. The only independent predictor of prognosis was the average number of mitoses per 2 mm<sup>2</sup> (10 HPF) [1].

Cytokines are hormone like polypeptides produced by many types of cells. They are the soluble mediators of inflammation and play a key role in immune reaction, tissue damage and loss of organ function. To our knowledge, TNF- $\alpha$ , IL-6 and IL-8 were synthesized and excreted from macrophages.

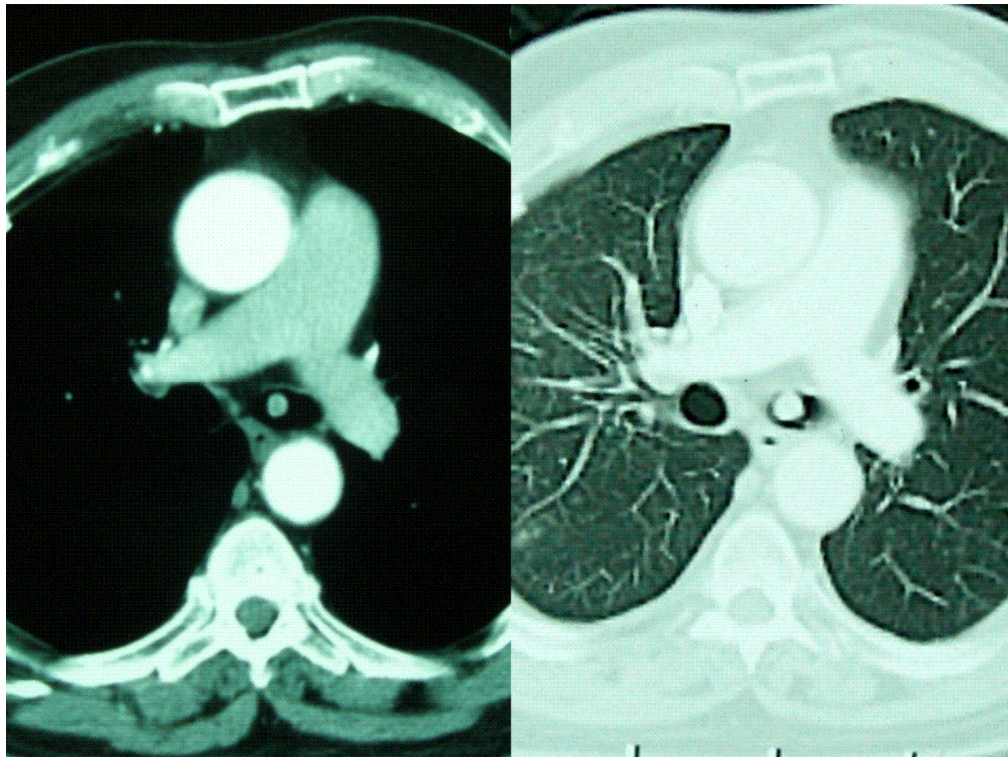
Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a pleiotropic cytokine which can be either

constitutively produced or induced in human tumors [2].

IL-8 is an important cytokine involved in pro-inflammatory and reparative processes [3]. IL-6 can be produced by airway epithelial cells and activates pulmonary macrophages in response to a variety of infectious agents and other inflammatory mediators [4].

## 2. CASE

A 71 year old male patient was admitted with cough and dyspnea. Breath sounds were decreased on left hemi-thorax at physical examination. Thorax computed tomography showed a 9 mm-sized lesion in anteromedial wall of the left main bronchus right next to the carina (Fig. 1).



**Fig. 1. Bronchial carcinoid tumor can be seen in left main bronchus on thorax tomography**

By fiber-optic bronchoscopy, it was seen that a vascular polypoidal lesion with no mucosal invasion obstructed the left main bronchus within 1.5 cm from carina. Routine laboratory tests were in normal ranges. Pulmonary function test was as FVC: 2.73 lt; FEV1: 1.69 lt /sc Fev1/FVC - 62% and it revealed bronchial obstruction. Informed consent was obtained before the operation.

Tumor became visible within the left main bronchus immediately after the bronchotomy was performed. Bronchial resection was carried out and surgical margins were tumor free at frozen section investigation. Bronchial resection and reconstruction was performed without lung resection.

Among the 1.7 cm sized bronchial resection specimen, the pathological evaluation revealed a 1-cm tumoral mass under the bronchial epithelium. No tumor necrosis was detected. It had a mitotic count of 2 in 50X magnification. In immunochemical staining; tumor cells were positive for chromogranin and cytokeratin. Also, there were tumor focuses stained with synaptophysin and CD56. The percentage of KI 67 positive cells was 2%. Tumor margins had benign cytological features. Bronchial lavage of the both lungs was carried out by the double-lumen endotracheal intubation, pre- and post-operatively, in order to evaluate the inflammation that bronchial carcinoid tumor caused. 20 ml saline solution was given through each bronchus and aspirated. TNF- $\alpha$ , IL-8 and IL-6 levels of each bronchial lavage sample were analyzed.

Preoperative TNF- $\alpha$  and IL-8 levels were found more than 2-folds and 5- folds higher respectively on the tumor side (TNF- $\alpha$ ; 14.18 pg/ml and IL-8; 3359.86 pg/ml) compared to tumor-free bronchial system (TNF- $\alpha$ ; 6.88 pg/ml, IL-8; 615.07 pg/ml). It was observed that both cytokine levels decreased to the level of tumor-free bronchial system values following bronchial resection and reconstruction.

There was no significant difference in IL-6 levels between two bronchial systems preoperatively (IL-6 right bronchus; 16.44 pg/ml, IL-6 left bronchus; 19.11 pg/ml); IL-6 levels showed more than four-fold increase postoperatively (IL-6; 89.41 pg/ml) (Fig. 2).

During the postoperative follow-up, no complications were confronted. Control bronchoscopies were performed at the 1st week and 3<sup>rd</sup> month after surgery. Suture line and

bronchial system was intact; and also no stenosis was observed (Fig. 3).

No complications have occurred during 19-month follow-up period.

### 3. DISCUSSION

The changes in the immune system can be monitored by measuring the levels of cytokines or the inflammatory mediators in the broncho-alveolar lavage [5]. Cytokine levels may alter due to infection, surgical operation or severity of the disease.

In our study, bronchial lavages were performed on both bronchial systems separately shortly before the operation to determine the cytokine response caused by carcinoid tumor and it was repeated on operated bronchus in the operation room in order to see the effect of bronchial resection and reconstruction on cytokine response.

The present study revealed that a well differentiated tumor such as carcinoid might cause an alteration in TNF- $\alpha$  and IL-8 levels. Tumor-stasis, retention of mucous and any possible distal infection were not considered as the cause of this cytokine activity because of their decrement up to normal ranges right after the operation. Current data in the literature show that increased serum concentration of IL-6 is a good marker of severity of surgical stress after thoracic cancer surgery [6]. To our knowledge, bronchial cytokine levels of carcinoid tumors have not been studied yet. It is difficult to collect samples from an identical group of carcinoids and/or operation types because of rarity of the cases. Study of cytokine levels in this case was prompted due to another research and it was selected because of its specialty and uniqueness. With this case, we aimed to draw the attention to this topic.

In this well-differentiated carcinoid case, it was seen that pro-inflammatory cytokines like TNF- $\alpha$  and IL-8 were secreted in significant amounts and they were found to decline to normal ranges postoperatively. Although, forming an opinion is difficult with a single case, we can say that carcinoid tumors might be activating the process of TNF- $\alpha$  and IL-8 secretion or secreting these cytokines themselves. The decrease of TNF- $\alpha$  and IL-8 levels to preoperative tumor-free bronchial system levels after the operation might be demonstrating that the main cause of this

cytokine response is actually the carcinoid tumor itself and could be a marker of successful resection.

IL-6 levels were not high in the preoperative course; but the post-operative levels seemed to

be elevated. The increase of IL-6 in serum has been shown in many studies based on post-operative responses. Hence, the bronchoplastic procedure could be the reason of escalated IL-6 response.

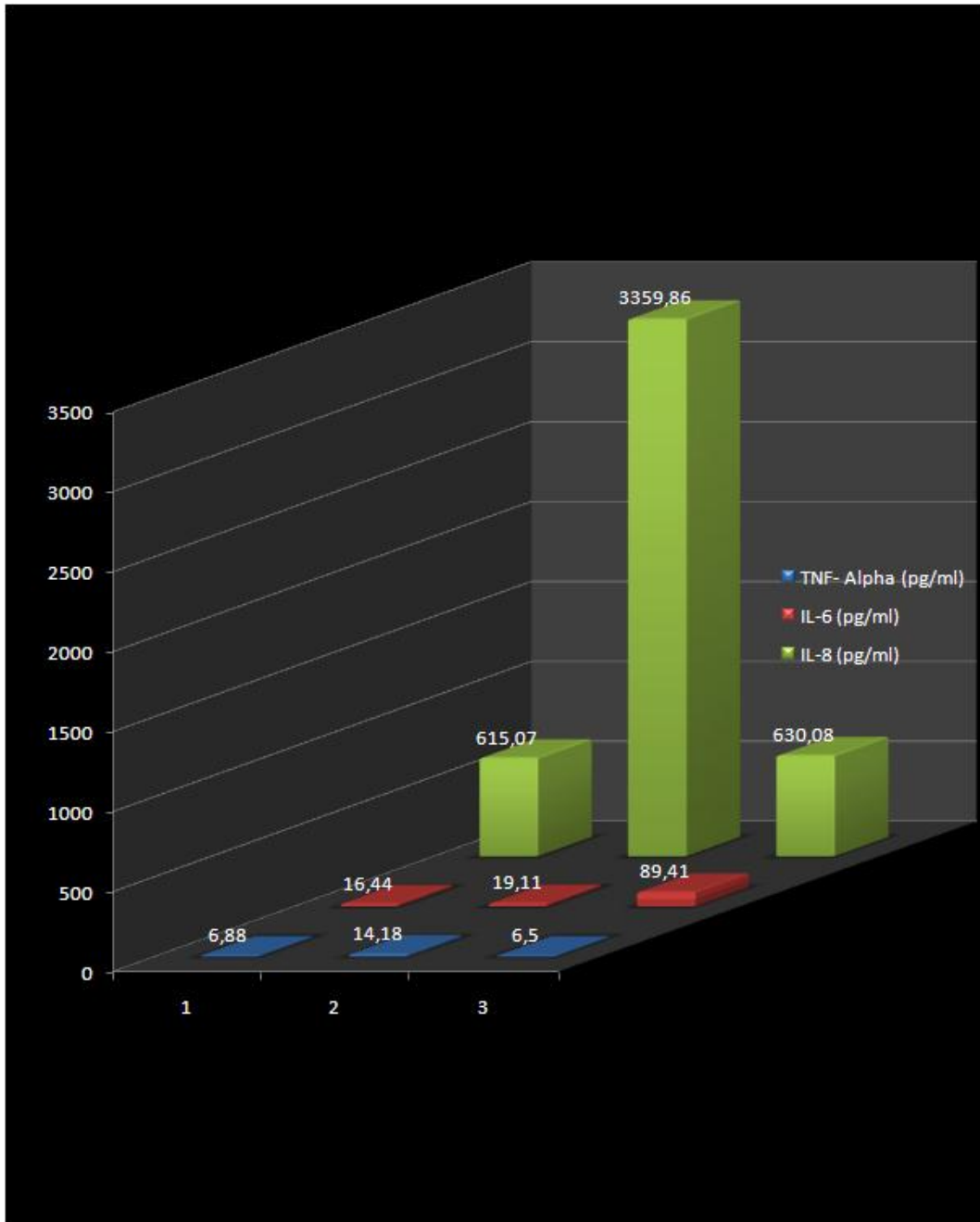
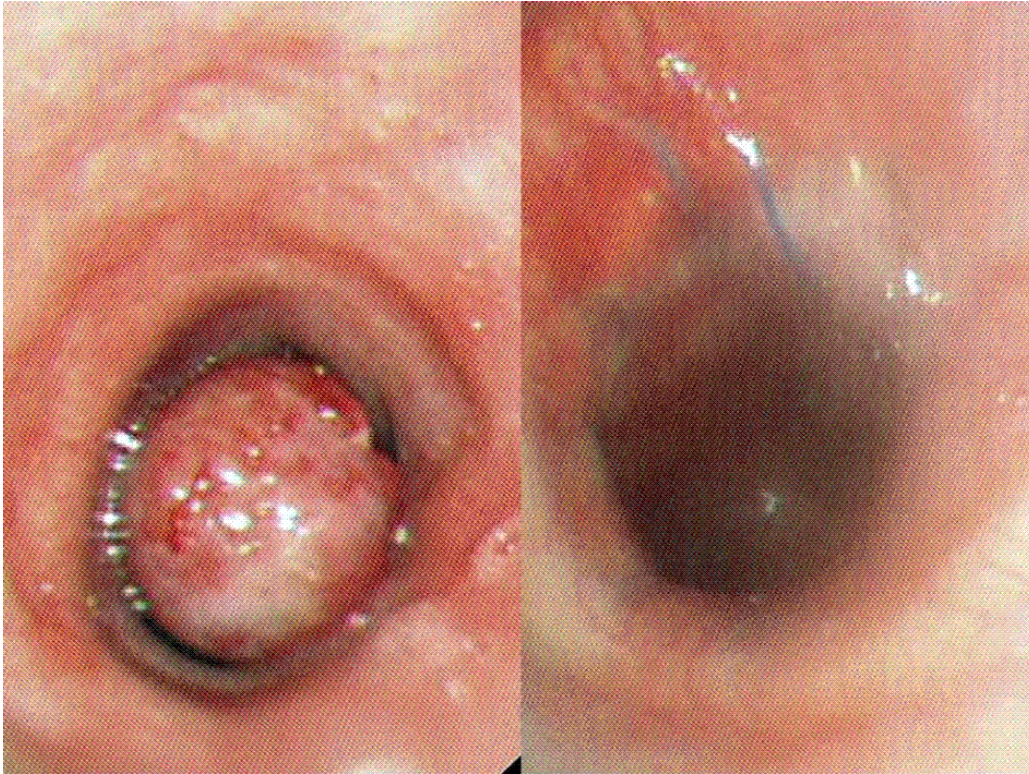


Fig. 2. (1) Preoperative tumor free bronchus, (2) Preoperative bronchus with tumor, (3) Postoperative bronchus which tumor resected



**Fig. 3. Vascular polypoidal lesion can be seen in left main bronchus on bronchoscopy (left); suture line was observed with bronchoscopy 3 months after surgery (right)**

#### **4. CONCLUSION**

In conclusion, the reduction of TNF- $\alpha$  and IL-8 levels up to normal bronchial cytokine levels suggests the conception that carcinoid tumors have a role in secretion of these cytokines. Also, it brings the idea to mind that detection of their levels might be beneficial in terms of determining the adequacy of resection and early detection of tumor recurrence.

As we mentioned before, with a single case it is impossible to come to a conclusion. However, the data of this case might contribute to the further studies on carcinoid tumors.

#### **ETHICAL APPROVAL**

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki

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#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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