Elevated Serum Levels of Tumor Necrosis Factor-α after Bronchoscopy and Bronchoalveolar Lavage*

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Fiberoptic bronchoscopy and bronchoalveolar lavage are often followed by the development of fever and other influenza-like symptoms. We report the onset of these symptoms in a healthy volunteer following bronchoscopy and bronchoalveolar lavage; the symptoms were temporally associated with the dramatic elevation of serum levels of tumor necrosis factor. Our observations suggest that tumor necrosis factor may be involved in mediating fever and other influenza-like symptoms occurring after bronchoscopy. (Chest 1991; 99:1529-30)

FOB = fiberoptic bronchoscopy; BAL = bronchoalveolar lavage; TNF = tumor necrosis factor; AM = alveolar macrophage

Bronchoscopy with BAL is frequently used in the evaluation of a number of diverse acute and chronic pulmonary diseases. The availability of the procedure and the relative ease in recovery of AMs by BAL have allowed intensive investigation into the cellular functions of these tissue phagocytes. In general, bronchoscopy is well tolerated, with a relatively low incidence of morbidity and mortality. Influenza-like symptoms, such as fever, myalgias, and headache, develop in as many as 3 to 50 percent of the subjects following bronchoscopy.1 4 The biologic factors attributable to these symptoms have not been fully characterized. Tumor necrosis factor-α is a mononuclear phagocyte-derived cytokine with a vast array of biologic effects,8-10 including the induction of hemorrhagic necrosis of certain tumors and functioning as an endogenous pyrogen; and is likely the major proximal mediator of septic shock.11 The intravenous infusion of TNF in humans results in similar influenza-like symptoms12 comparable to that observed in the period after bronchoscopy. We now report the delayed development of fever, chills, headache, and myalgias in a patient undergoing BAL, symptoms which temporally correlated with the presence of systemically detectable TNF levels.

**Case Report**

A normal male volunteer agreed to undergo bronchoscopy with BAL as part of a research protocol for the investigation of cytokine expression from human AMs. The subject had been well without symptoms suggestive of infection in the preceding six weeks and was not receiving any medication. The individual was premedicated with atropine (1 mg) IM and the airway topical anesthetized with 2 percent lidocaine. The fiberoptic bronchoscope was wedged into two different subsegments of the right middle lobe, followed by instillation of 300 ml of sterile normal saline solution. Recovered fluid measured 265 ml and was obtained without complications. Symptoms and body temperature were recorded for 48 hours following the procedure. In addition, samples of serum were obtained from the subject immediately before bronchoscopy and at 4, 12, 20, 36, and 48 hours after BAL. Serum TNF bioactivity was assessed using the WEHI 164 subclone 13 bioassay, with a limit of sensitivity to 35 pg/ml of TNF.13 The subject was well until 12 hours after BAL, at which time the onset of headache and myalgias were noted. These symptoms persisted for 8 hours, at which time the subject experienced chills, fever (38.0°C), worsening headache, and associated right-sided pleuritic chest pain. The signs and symptoms gradually abated over the subsequent 12 hours, and the subject was free of symptoms by 48 hours after bronchoscopy. As shown in Figure 1, a dramatic time-dependent increase in serum TNF levels was detected during the time period observed. Serum TNF levels were undetectable (less than 35 pg/ml) prior to BAL, rose as early as 4 hours after BAL, and peaked at 24 hours (1,200 pg/ml) after the procedure. The serum levels of TNF persisted for 36 hours (353 pg/ml), with a decline to undetectable levels by 48 hours after BAL.

**Discussion**

The performance of bronchoscopy with BAL is associated with a low incidence of complications and is generally well tolerated.1 Fiberoptic bronchoscopy on occasion can precipitate laryngeal stridor and bronchospasm, which can be rapidly reversed with the administration of SQ epinephrine or inhaled β-adrenergic agonists. In addition, mild chest discomfort 12 to 24 hours following BAL can occur. Pneumothorax induced by BAL, although uncommon, has been reported.12 The incidence of fever following bronchoscopy has varied considerably between series. An earlier study reported fever in 46 percent of the patients undergoing rigid
bronchoscopy, one third of which had positive blood cultures during the peribronchoscopic period. Subsequent investigations have suggested that the incidence of fever associated with FOB is significantly lower than that observed after rigid bronchoscopy. In two studies of over 350 patients undergoing FOB, the incidence of fever was only 2.5 percent to 16 percent. The majority of these patients developed fever during the first 24 hours after FOB, while none of the patients was found to have positive blood cultures. The mechanism for this fever was unclear, and it was attributed to either atelectasis or infection produced by organisms present in the airway at the time of the procedure. We now report the presence of significant systemic TNF levels in a patient after FOB and BAL which temporally correlated with the development of influenza-like symptoms, including fever, chills, myalgias, and headache.

Tumor necrosis factor-a is a 17 kD MW polypeptide with diverse pleiotropic effects on a variety of cell types. It has a major role in host defense against cancer and infection, as this critically important cytokine is instrumental in the generation of an inflammatory response. Moreover, TNF is the major proximal mediator of endotoxin-induced septic shock. Elevated serum levels of TNF have been detected in normal subjects after an injection of endotoxin (4 ng/kg), with maximal TNF levels (240 ± 70 pg/ml) achieved 2 hours after endotoxin infusion, declining to unmeasurable levels by 4 hours. All patients experienced influenza-like symptoms, including fever, chills, myalgias, and headache, with maximal fever coinciding with peak serum levels of TNF. Another endogenous pyrogen, interleukin 1, was not found in the serum of these patients. The intravenous administration of TNF to patients with cancer is associated with fever in nearly all subjects, first noted within 1 to 2 hours after the initiation of TNF therapy. Therefore, it is consistent that TNF generation after FOB and BAL is capable of mediating the signs and symptoms observed in this subject.

The cellular source or sources of TNF generation in this subject after FOB and BAL remain open for speculation. The AM, interstitial pulmonary macrophage, or newly recruited mononuclear phagocytic cells are the most likely sources. In addition, recruited T-lymphocytes and systemically activated peripheral blood monocytes may also contribute to the circulating levels of TNF. Although there was no evidence for acute bacterial infection in this subject, bacterial products (e.g., endotoxin) may have served as a triggering stimulus for immune cell-derived TNF production. As we have not as yet measured serum TNF levels in patients who do not develop fever or other symptoms after BAL, we cannot definitively establish a cause-and-effect relationship between elevated circulating TNF levels and the development of symptoms. Nonetheless, the magnitude of the TNF response in the context of what is known about the systemic effects of TNF make such a relationship likely. In light of these intriguing observations, future controlled trials investigating the role of TNF in mediating the fever and influenza-like symptoms after FOB and BAL seem warranted.

REFERENCES