Mechanism of Mucin Secretion in Diffuse Panbronchiolitis

To the Editor:

We read with interest the article by Kim et al in CHEST (September 2004) in which the authors examined the relationship between epidermal growth factor receptor (EGFR) expression in the bronchiolar epithelium with neutrophilic inflammation and mucus hypersecretion in the tissues of patients with diffuse panbronchiolitis (DPB). DPB is a COPD that is characterized clinically by chronic cough, excessive sputum, and dyspnea. It is prevalent in Japan and Korea but is rare in other countries. If left untreated, DPB is fatal. The introduction of low-dose, long-term prednisolone has markedly improved the prognosis of DPB patients and survival, and it is now an accepted treatment. Over the past decade, many studies have concentrated on the mechanisms of mucus hypersecretion in DPB, and its relation to the EGFR-mucin pathway should be acknowledged. However, several points of weakness in their study should be debated.

First, it is known that in healthy lungs few cells will be positively stained with alcian blue-periodic acid-Schiff (AB/PAS) stains. The markedly high percentage of mucin staining in the bronchial epithelium of the control samples in this study (50%) indicate clearly that there was something wrong with these samples. The authors mention that the samples were taken from healthy portions of the lobeectomy specimens from six nonsmoking patients with adenocarcinoma. It seems that even the uninvaded lung tissues of the adenocarcinoma patients were showing secondary changes, so clearly these patients were not the proper control subjects. The authors could use the easier option of collecting fiberoptic bronchoscopic bronchial biopsy specimens from completely healthy volunteers.

Second, Figure 7 seems to contradict what is written in the results and is shown in Figure 4. While in the results it is written that the mean ± SD percentage of the luminal area occupied by AB/PAS and MUC5AC stains was 84.6 ± 7.63% in the DPB group, which is beautifully shown in Figure 4; Figure 7 shows hardly any intraluminal mucin or MUC5AC staining in either group.

Third, in the control subjects, the finding that 50% of the bronchiolar epithelial area was occupied by epithelium stained with AB/PAS and MUC5AC while EGFR expression was absent is difficult to understand. It had been shown that the airway mucin production in response to various stimuli is mediated through the EGFR cascade. EGFR was shown to be related to mucus secretion in goblet cells, not to the degranulation of the mucin granules. The authors’ assumption that goblet cell hyperplasia occurred due to some transient inflammation, and that degranulation did not occur due to inflammation subsidence, which led to a down-regulation of EGFR, is too hypothetical, and it only indicates that these were not suitable control samples.

In conclusion, we think that another, better controlled prospective study that will also examine the BAL fluid for counts of neutrophils and other cells, as well as for cytokines such as interleukin-8, and their correlation to the EGFR expression and mucous secretion is still needed.

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To be continued.

REFERENCES


Plasma Levels of N-Terminal Pro-Brain Natriuretic Peptide in the Critically Ill

The Right Hormonal Marker in the Wrong Patients?

To the Editor:

A recent article by Jefic and coworkers (July 2005) on the utility of N-terminal pro-brain natriuretic peptide (NTproBNP) for estimation of pulmonary artery occlusion pressure (PAOP) in critically ill patients concluded that NTproBNP may be a strong discriminator of cardiac dysfunction in these patients. The authors observed inverse correlations between NTproBNP and cardiac index and left ventricular stroke work index (LVSWI) but not between NTproBNP and PAOP. This suggests that, in contrast to patients with heart failure, other factors than the physiologic stimulus ventricular stretch may be involved: the accompanying disease process (sepsis, surgery and pharmacologic factors).

We have shown that 15 mL/kg of NaCl 0.9% IV induces a 250% increase in NTproBNP levels in volunteers. The patients of Jefic et al will have been treated with a much higher volume/sodium load and, additionally, many drugs that have not been studied yet regarding effects on NTproBNP. Thus, the correlations between NTproBNP, cardiac index, and LVSWI may be an epiphenomenon of underlying disease and therapy, and increased NTproBNP levels in these patients should better be interpreted as signs of multiorgan dysfunction instead of cardiac dysfunction.

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Dr. Heringlake has received and continues to receive support by Roche Diagnostics, Germany (manufacturer of NTproBNP kits and analyzers), in the form of analytical materials and costs for external analyses.
To the Editor:

We appreciate the comments of Dr. Heringlake and colleagues. In our study, we initially asked whether levels of brain natriuretic peptide (BNP) and N-terminal probrain natriuretic peptide in patients with severe sepsis. Circulation 2005; 112:527–534


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Idiopathic Chronic Cough and Organ-Specific Autoimmune Disease

To the Editor:

In a recent article in CHEST (May 2005), Mund et al1 described 11 female patients with idiopathic chronic dry-cough, with onset occurring around the menopause, that was associated with an increase in absolute lymphocyte count in BAL fluid. We have also previously described2 a lymphocytic bronchoalveolitis in patients with idiopathic chronic dry-cough and have noted the onset of cough around the age of menopause. In our experience, these patients have an increased prevalence of organ-specific autoimmune disease, particularly hypothyroidism.2,3 We have suggested that the cough may be the result of the aberrant honing of activated lymphocytes to the airways in a manner analogous to the airway diseases seen with inflammatory bowel disease.4 Support for this view is provided by our findings that patients with treated hypothyroidism have an increased prevalence of cough, a heightened cough reflex sensitivity, and evidence of low-grade airway inflammation.4,5 It is not clear from the study presented by Mund et al whether their patients with idiopathic cough were asked specifically about the presence of organ-specific autoimmune disease and whether autoantibodies were measured. Further immunopathologic studies are required to identify novel therapeutic targets for this troublesome condition.

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To the Editor:

We appreciate very much the comments by Birring and Pavord on our article in CHEST (May 2005).1 In our study, we described a condition characterized by dry cough and a lymphocytic bronchitis dominated by activated CD4+ cells. Apart from dry cough, all patients were, according to the inclusion criteria, otherwise asymptomatic and were not receiving regular treatment with drugs. This condition, which was characterized by dry cough as the only symptom, was found only in women, and it seemed to have commenced in connection with an airway infection that coincided with the menopause. Although we did not take specific diagnostic measures in order to prove the existence of hypothyreosis, diabetes mellitus, pernicious anemia, inflammatory bowel disease, Sjögren syndrome, or other autoimmune conditions, no patients had symptoms that led us into the suspicion of organ-specific autoimmune diseases. We agree that further immunopathologic studies are required for a more detailed identification of the condition. It is an intriguing thought that the described “dry cough condition” is mediated by autoimmune mechanisms and that infections during menopause may

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