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Bronchoalveolar Cellularity and Interleukin-8 Levels in Measles Bronchiolitis Obliterans*

Young Yull Koh, MD; Da Eun Jung, MD; Ji Yeon Koh, MD; Jung Yeon Kim, MD; Young Yoo, MD; and Chang Keun Kim, MD

**Background:** Measles virus infection may progress to a chronic obstructive process including bronchiolitis obliterans (BO). This study investigates pulmonary cellular profiles and interleukin (IL)-8 levels in patients with BO following the measles.

**Methods:** BAL fluid was obtained from 12 children with BO who had a history of measles pneumonia during an outbreak in 2000 and 2001. BAL cell counts and differentials were compared to control patients as well as BAL IL-8 levels, which were measured by enzyme-linked immunosorbent assay. Immunohistochemical staining of BAL cells and three open-lung biopsy specimens were also analyzed for T-cell surface markers CD3, CD4, and CD8.

**Results:** BAL cellular profiles were characterized by a significantly increased percentage of neutrophils in the measles BO group (median, 16.0%) compared to the control group (2.3%) \(p < 0.01\). BAL IL-8 levels were also markedly increased in the measles BO group (mean ± SD, 418.6 ± 286.0 pg/mL) compared to the control group (92.8 ± 126.7 pg/mL) \(p < 0.01\). BAL IL-8 levels correlated significantly with neutrophil percentages in both the measles BO group (\(r = 0.86, p = 0.000\)) and the control group (\(r = 0.79, p = 0.007\)). The lymphocyte subsets were characterized by a significantly increased number of CD8+ cells, resulting in a decreased CD4/CD8 ratio in the BAL and the biopsy specimens.

**Conclusion:** These results suggest that pulmonary neutrophils and IL-8, along with CD8+ T lymphocytes may play an important role in the pathogenesis of BO after measles virus infection.

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**Key words:** bronchiolitis obliterans; CD8; interleukin-8; measles; neutrophils

**Abbreviations:** BO = bronchiolitis obliterans; HRCT = high-resolution CT; IL = interleukin; IQR = interquartile range

Measles virus infection is still a common illness in many parts of the world.1,2 The most common complication of this disease is pneumonia, either primary measles viral pneumonia or secondary bacterial pneumonia.3,4 Measles pneumonia is a potentially life-threatening complication in children with the measles virus. Measles virus infection may progress to a chronic obstructive process including bronchiolitis obliterans (BO), also referred to as constrictive bronchiolitis, a rare pulmonary disorder characterized histologically by an inflammatory/fibrosing process that constricts and ultimately obliterates the small airways. The functional loss of these airways results in the insidious development of chronic cough and prolonged wheeze, often progressing to severe respiratory distress. During the

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last decade, high-resolution CT (HRCT) of the thorax in patients with chronic respiratory symptoms has enhanced the ability of clinicians to identify BO noninvasively. Our current knowledge of BO after measles infection is based largely on case reports and a few small series of patient studies in older literature.

BAL is a valuable research tool for the assessment of cellular and noncellular components of lower respiratory tract inflammation. Thorough analysis of the BAL fluid cellular profile can be a valuable method for deciphering the pathogenesis of airway disorders. Previously, we have shown an increased percentage of BAL neutrophils in BO that was preceded by an infection of adenovirus or Mycoplasma pneumoniae. However, there are no previously published reports of the cellular analysis of BAL fluid from BO after measles. A thorough literature search failed to reveal any reports documenting airway immunologic changes, such as changes in CD4 or CD8 populations in the lung after measles pneumonia. Neither have there been reports of specific chemotactic factors such as interleukin (IL)-8 with airway inflammation for postinfectious BO.

To our knowledge, this is the first study to investigate the pathogenesis of BO after measles infection by analyzing cell differentials in BAL fluid. We tried to determine whether neutrophils were increased in postmeasles BO, as they have been described in other patients with postinfectious BO. Furthermore, IL-8, a major chemotactic factor for neutrophils, was examined in order to determine the levels in postmeasles BO.

**METHODS AND MATERIALS**

**Measles BO Subjects**

Study subjects had compatible clinical presentations and at least one diagnostic indicator of BO in addition to a history of measles pneumonia during a measles outbreak that occurred in 2000 and 2001 at two university medical centers in Korea (Inje University Sanggye Paik Hospital and Seoul National University Hospital, both in Seoul, South Korea). Twelve previously healthy infants with a minimum of three episodes of wheezing after measles pneumonia were recruited. All the subjects were extensively evaluated and treated by their primary care physicians and pulmonologists without resolution of their symptoms. Patients with persistent respiratory symptoms, despite multiple interventions and evaluations, then underwent bronchoscopic evaluation. Allergy test results were all negative.

Initially, 19 subjects with wheezing after measles infection were enrolled. However, seven patients were excluded due to one of the following reasons: history of asthma (n = 3), atopic dermatitis (n = 1), and positive response to conventional bronchodilator therapy (n = 3).

**Diagnosis of Measles Pneumonia:** Diagnostic criteria for measles pneumonia included the following: (1) clinical diagnosis with all of the following: generalized maculopapular rash lasting > 3 days, temperature > 38.3°C, and the three “Cs”: cough, coryza, and conjunctivitis; (2) serologic (IgM antibody) confirmation of the disease; and (3) pneumonia confirmed by standard chest radiography.

**Diagnosis of Postmeasles BO.** In addition to a positive diagnosis of measles pneumonia, a diagnosis for postmeasles BO included the following (1): HRCT demonstrating a unilateral hyperlucent lung and/or a combination of geographic hyperlucency, bronchectasis, bronchial thickening, and vascular attenuation; or (2) diagnosis of BO by lung biopsy.

**Control Subjects**

Ten children undergoing elective surgery requiring general anesthesia (ie, hernia, skin graft) who had no history of acute (< 1 month) or chronic respiratory symptoms served as control subjects. All subjects were children of Korean descent. Korea has a racially homogenous society. The socioeconomic status of the study population and the control group was low-to-middle class. Parents of the BO patients and the parents of the control subjects gave informed consent, and the Hospital Institutional Review Boards approved this study.

**Flexible Bronchoscopy With BAL**

All control subjects were evaluated by flexible bronchoscopy with a BAL in an operating room setting under general anesthesia through an endotracheal tube while under the direct supervision of an anesthesiologist. An endotracheal tube with a minimum of 4.5 mm in diameter and a 3.6-mm fiberoptic bronchoscope with a lavege port were used to allow adequate airflow. All measles BO subjects were evaluated with a 3.6-mm pediatric flexible bronchoscope (Olympus BF-3G30: Olympus; Tokyo, Japan). Bronchoscopy with BAL was performed according to previously described guidelines. Nebulized albuterol was prescribed uniformly for all the subjects before the procedure. Premedication consisted of IM atropine sulfate (0.01 to 0.02 mg/kg) and IV midazolam (0.1 to 0.2 mg/kg). During bronchoscopy, oxygen was readily available, and each patient had an IV access. Heart rate and transcutaneous arterial oxygen saturation were monitored throughout the procedure. The bronchoscope was inserted transnasally, and lidocaine (2%) was delivered directly onto the vocal cords before passage into the lungs. After examination of the upper and lower airways, the tip of the bronchoscope was wedged into a segmental or subsegmental bronchus of the right middle lobe or left lower lobe. Three 1.0 mL/kg aliquots of 0.9% sterile isotonic saline solution were instilled through the instrumentation channel. Each aliquot was immediately aspirated into a sterile specimen container by using a wall suction pressure of 100 to 150 mm Hg. Aspirated BAL fluid was pooled together into a single specimen and immediately placed on ice.

**Processing and Analysis of BAL Fluid**

The total amount of recovered fluid was measured, and the recovery was calculated as a percent of the volume instilled. Pooled BAL fluid was separated into two aliquots. One aliquot was submitted for viral and bacterial cultures to the Hospital Microbiology Department. The remainder was analyzed in the laboratory for cellular and fluid proteins. The BAL fluid analyzed in the laboratory was first centrifuged at 400g for 10 min at 4°C to separate fluid from cells. Total cell counts were performed using a hemocytometer (Weber; Teddington, UK). Differential counts were obtained from a cytospin (Shandon; Pittsburgh, PA) slide.
preparations by using a May-Grunwald-Giemsa stain and by figuring a percentage from 400 cells. The cell-free fluid was frozen at −70°C until required for IL-8 assay.

**Immunohistochemistry**

Immunohistochemical staining of BAL cells and three-open lung biopsy specimens were carried out on direct smear and paraffin-embedded sections by using the avidin-biotinylated peroxidase complex method. The following detection antibodies were used: anti-CD3 monoclonal antibody (1:100; DAKO; Carpenteria, CA), CD4 (1:40, Novocastra; Newcastle, UK), and CD8 (1:40; Novocastra). Positive and negative controls were used. The slides were examined using conventional light microscopy. Cells with moderate-to-intense nuclear stain were considered positive.

**IL-8 Assay**

IL-8 levels were measured by using a commercial enzyme-linked immunosorbent assay (Endogen; Woburn, MA). The kits were able to detect concentrations as low as 2 pg/mL of IL-8. All samples were run in duplicate, and the mean values were used for statistical analysis.

**Statistical Analysis**

IL-8 levels in BAL fluid were expressed as mean ± SD. Cellularity data were expressed as the number per milliliter of BAL fluid (total cell count) or as a percentage of the total WBC count (cell differential) and were presented as medians with an interquartile range (IQR). All other results were presented as medians and ranges. Differences between the two groups were determined by using the nonparametric Mann-Whitney U test. Positive and negative controls were used. The slides were examined using conventional light microscopy. Cells with moderate-to-intense nuclear stain were considered positive.

**Results**

**Patient Characteristics**

The baseline characteristics of subjects studied are shown in Table 1. There were no statistical differences between the two groups in terms of age, sex ratio, and blood eosinophils. Most patients had typical symptoms, such as coughing, wheezing, exercise intolerance, and frequent respiratory illnesses. The most common physical finding was wheezing. Clubbing was noted in only one patient. BAL cultures from two patients (one male and one female) grew *Moraxella catarrhalis*, although neither patient had clinical findings suggestive of an acute infection prior to or at the time of bronchoscopy. In this series, therapeutic agents typically used in the treatment of asthma were prescribed. Ten patients received albuterol, 5 patients received inhaled corticosteroids, 1 patient received oral glucocorticoids, and 3 patients received theophylline.

**Procedure-Associated Complications**

Bronchoscopy with BAL was relatively well tolerated by all subjects. Minor procedure-associated complications occurred on nine occasions, comprising transient hypoxia (*n* = 2) and minor epistaxis (*n* = 1). These complications, however, did not preclude the completion of the procedure. One child had a transitory hoarse cough and a low-grade fever up to 38°C occurring within 12 h of the procedure. Each of these relatively minor adverse events spontaneously resolved within 24 h.

**BAL Cell Profiles**

The absolute number of BAL cells, and the cell percentages, including lymphocyte subsets, are shown in Table 2. The total cell number was significantly higher in the measles BO group compared to the control group (*p* < 0.05). The differential cell counts were characterized by a significant increase of neutrophils in the measles BO group than in the control group: median, 16.0% (IQR, 4.3 to 56.5%) vs 2.3% (IQR, 1.0 to 3.9%), respectively (*p* < 0.01). The percentage of macrophages was lower in the measles BO group than in the control group, in conjunction with a marked increase in the percentage of neutrophils. There were no significant differ-

**Table 2—Differential Cytology and Lymphocyte Subsets of BAL Fluid**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Measles BO (n = 12)</th>
<th>Control (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cells, 10⁶/mL</td>
<td>38.5† (18.2–159.0)</td>
<td>15.6 (7.9–18.1)</td>
</tr>
<tr>
<td>Macrophages, %</td>
<td>71.0† (40.8–84.3)</td>
<td>85.0 (81.5–89.0)</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>4.0 (1.0–10.0)</td>
<td>7.5 (5.0–10.8)</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>16.0† (4.3–56.5)</td>
<td>2.3 (1.0–3.9)</td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td>0.0 (0.0–0.8)</td>
<td>0.0 (0.0–0.1)</td>
</tr>
<tr>
<td>Epithelial cells</td>
<td>3.5 (2.3–4.2)</td>
<td>3.2 (1.7–9.9)</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+, %</td>
<td>88.0 (84.0–91.8)</td>
<td>82.0 (78.0–88.5)</td>
</tr>
<tr>
<td>CD4+, %</td>
<td>23.3 (23.0–34.0)</td>
<td>28.0 (28.0–34.0)</td>
</tr>
<tr>
<td>CD8+, %</td>
<td>62.0† (55.0–65.0)</td>
<td>46.0 (38.5–50.5)</td>
</tr>
<tr>
<td>CD4/CD8 ratio</td>
<td>0.41† (0.36–0.55)</td>
<td>0.65 (0.57–0.79)</td>
</tr>
</tbody>
</table>

*Data are expressed as median (IQR) [25th–75th].
†p < 0.05 compared with control.
‡p < 0.01 compared with control.

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\*At the time of BAL.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Measles BO</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr†</td>
<td>3.0 (1.0–5.2)</td>
<td>3.1 (1.7–4.1)</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>9:3</td>
<td>7:3</td>
</tr>
<tr>
<td>Blood eosinophils, /µL‡</td>
<td>145 (10–740)</td>
<td>170 (26–231)</td>
</tr>
<tr>
<td>Interval from measles to BAL, mo‡</td>
<td>6.0‡ (4.0–15.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are expressed as median (range) or No.
†p < 0.05 compared with control.
‡p < 0.01 compared with control.

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ences in percentages for the lymphocytes, eosinophils, and epithelial cells between the two groups.

The lymphocyte subsets were characterized by a significantly increase of percentage of CD8+ cells in the measles BO group (median, 62.0%; IQR, 55.0 to 65.0%; p < 0.01), compared to the control group (median, 46.0%; IQR, 38.8 to 50.5%), resulting in a significantly decreased CD4/CD8 ratio in the measles BO group (median, 0.41; IQR, 0.36 to 0.55; p < 0.01) compared to the control group (median, 0.65; IQR, 0.57 to 0.79).

BAL was performed in three patients who had measles infection during the outbreak but in whom measles pneumonia or postmeasles BO did not develop. These three patients underwent elective surgery 7 to 10 months later, and the BAL was performed in an operating room setting under general anesthesia through an endotracheal tube. The differential cell count in BAL fluid revealed a normal differential (median, 80.0% macrophages, 8.0% lymphocytes, 4.0% neutrophils, 0% eosinophils, 1.5% epithelial cells of the total) as well as normal lymphocyte subsets (83% CD3, 28% CD4, 47% CD8, 0.60 CD4/CD8 ratio).

**BAL IL-8 Levels**

IL-8 levels in BAL fluid are shown in Figure 1. Subjects in the measles BO group, as compared with the control group, had significantly elevated IL-8 levels (mean ± SD, 418.6 ± 286.0 pg/mL vs 92.8 ± 126.7 pg/mL; p < 0.01).

We investigated correlations between IL-8 levels and neutrophil percentages in BAL fluids. BAL IL-8 levels correlated significantly with BAL neutrophil percentages in the measles BO group (r = 0.86, p = 0.000) and in the control group (r = 0.79, p = 0.007), respectively (Fig 2). There were no observed significant relationships between BAL IL-8 levels and lymphocyte subsets (CD3, CD4, or CD8) in BAL fluid.

**HRCT and Lung Biopsy**

Open-lung biopsy was performed on three subjects and compared to HRCT findings for correlations with the histologic findings (Fig 3). Histologic sections demonstrated bronchial dilatation, filling of broncholar lumen with inflammatory exudate, and peribronchiolar inflammatory cell infiltrations. In these patients, mosaic attenuation, bronchiectasis, wall thickening, and decreased vascularity were seen on HRCT.

**Immunohistochemistry**

Immunohistochemical profiles of the open-lung biopsy specimens demonstrated that the peribronchiolar inflammatory cells express CD3 and CD8 but no detectable CD4 (Fig 4).

**Discussion**

To our knowledge, this is the first reported BAL study of postmeasles BO. This study investigated the cytologic and immunophenotypical profiles as well as
BAL fluid IL-8 levels in patients with postmeasles BO. The cellular profile indicates a neutrophil accumulation and an increase of CD8+ cells. BAL IL-8 levels were also markedly increased. BAL IL-8 levels correlated significantly with BAL neutrophil percentages. Immunohistochemical profiles of the lung biopsy specimens demonstrated the peribronchiolar inflammatory cells expressing CD3, CD8, but not CD4. Thus, these findings suggest that pulmonary neutrophils and IL-8 along with CD8+ T-lymphocytes may play an important role in the pathogenesis of postmeasles BO.

Measles is a respiratory disease beginning with infection in the upper respiratory tract and the conjunctivae. All epithelial cells of the respiratory tract from the nasal mucosa to the bronchioles are inflamed. With the use of measles vaccine, a dramatic decline in both morbidity and mortality has been achieved in many countries including Korea. The causes of the nationwide epidemic of measles in Korea during 2000–2001 despite the existence of an effective and safe vaccine are not fully understood. The most significant factor was thought to be the loss of “herd immunity” against measles as a combined result of the following: (1) insufficient vaccination coverage, (2) primary/secondary vaccine failure, (3) inherent disadvantages of the live attenuated vaccine, and (4) the interference by maternal antibodies.13

![Figure 3. Correlation of abnormal HRCT findings with histologic findings in a 24-month-old boy. Left, A: HRCT scan 8 months after measles of lower lobe bronchus demonstrating mosaic attenuation, bronchiectasis, and wall thickening. Right, B: Histologic section of the right lower lobe (hematoxylin-eosin, original × 200). Bronchial dilatation, filling of bronchiolar lumen with inflammatory exudate, and peribronchiolar inflammatory cell infiltrations (arrow) are noted.](image)

![Figure 4. Immunohistochemical staining of measles BO. The peribronchiolar inflammatory cells express CD3 (top, A) [arrow] and CD8 (bottom right, C) [arrow] but not CD4 (bottom left, B).](image)
A definitive diagnosis of BO is traditionally made with histopathologic confirmation via lung biopsy. Lung biopsy findings in our three children were consistent with “bronchiolitis obliterans.” However, this procedure is invasive and does not always confirm the diagnosis, because of the “patchy” distribution of airway involvement. During the last decade, HRCT for patients with respiratory diseases has enhanced the ability of clinicians to noninvasively identify BO. Consequently, a diagnosis of BO can be made with adequate noninvasive evidence from HRCT findings. The diagnosis of postmeasles BO in the present study is therefore considered to be accurate.

Two ethnically distinct populations of children, Maoris in New Zealand and Amerindians in Manitoba and South America, have been reported to be particularly susceptible to BO, suggesting that genetic or environmental factors may be important. Furthermore, genetic polymorphisms have been described that may infer increased susceptibility to the development of BO. In the present study, all BO subjects were children of Korean descent. Korea has a racially homogeneous society. There is no evidence that Koreans are more susceptible to postinfectious BO.

Technical difficulties and ethical considerations understandably limit the use of bronchoscopy and BAL with infants and children. The study subjects were children of Korean descent. Korea has a racially homogeneous society. There is no evidence that Koreans are more susceptible to postinfectious BO.

The use of corticosteroids and bronchodilators in chronic lung disease, including BO, after viral infection is controversial. Corticosteroid therapy in the early phase of BO has been proposed as modifier of the fibroblastic response. The use of bronchodilators is also controversial because of the theoretical lack of effect with fixed airway obstruction. In our study, there was no evidence that bronchodilators or corticosteroids had any effect on wheezing and coughing. The preponderance of neutrophils in the airways of postmeasles BO may explain, at least in part, the lack of clinical effect of corticosteroid treatment. Corticosteroids may also inhibit neutrophil apoptosis; and for such reasons, this type of chronic airflow obstruction is currently managed symptomatically. Therefore, no universally accepted levels of IL-8 were found in the measles BO group. Furthermore, IL-8 levels correlated significantly with neutrophil percentages in the BAL fluid. The cellular sources of IL-8 are unknown, but airway epithelial cells are a likely source. Activated neutrophils are directly cytotoxic to endothelial and epithelial cells via neutrophil-derived proteolytic enzymes, such as elastase and collagenase. Immunohistochemical studies in our subjects have demonstrated an increase in cytotoxic (CD8+) T-cells in peribronchial inflammation. It is quite possible that this T-lymphocytic inflammation precedes fibrous obliteration of bronchioles through peribronchial collagen deposition. Airway CD8+ T-cells, as well as neutrophils, therefore may play an important role in sustaining peripheral airway damage and fibrotic remodeling after measles infection.

The pathogenesis of BO has been studied extensively in the posttransplant population of patients and to a lesser degree in nontransplant cases. In posttransplant BO, bronchiolar epithelial cells are damaged, and T-lymphocytes and neutrophils are recruited to the site of injury. Vast arrays of cytokine and chemokine networks (those implicated include tumor necrosis factor-α, IL-2, IL-8, RANTES [regulated upon activation, normal T-cell expressed and secreted], platelet-derived growth factor, transforming growth factor, and fibroblast growth factor) are activated, perpetuating an inflammatory response. In the investigation of pathogenic mechanisms involved in adenovirus infection, Mistchenko et al found that high serum values for IL-6, IL-8, and tumor necrosis factor-α are associated with severity of adenovirus infection. The results of the present study, together with the above mentioned studies, suggest a common immunologic response independent of the etiology.

Levels of IL-8 were found in the measles BO group. Furthermore, IL-8 levels correlated significantly with neutrophil percentages in the BAL fluid. The cellular sources of IL-8 are unknown, but airway epithelial cells are a likely source. Activated neutrophils are directly cytotoxic to endothelial and epithelial cells via neutrophil-derived proteolytic enzymes, such as elastase and collagenase.

Evidence suggests that the first lavage aspirate contains the highest cytokine concentrations and sequential aspirates have decreased concentrations of acellular components. However, the first aspirate volume is quite variable and small and may represent more of a bronchial lavage, whereas succeeding aspirates are thought to represent a more distal alveolar lavage. Hence, for this study, it was considered acceptable to pool all lavagates, including the first BAL aliquot, for IL-8 analysis.

The increased number of neutrophils in BAL fluid from patients with postmeasles BO is similar to that found in case series of subjects with BO due to other conditions. The present study suggests an underlying role for IL-8 as a potent chemoattractant and activator for neutrophils because markedly elevated levels of IL-8 were found in the measles BO group. Furthermore, IL-8 levels correlated significantly with neutrophil percentages in the BAL fluid. The cellular sources of IL-8 are unknown, but airway epithelial cells are a likely source. Activated neutrophils are directly cytotoxic to endothelial and epithelial cells via neutrophil-derived proteolytic enzymes, such as elastase and collagenase.
protocol has been established for the treatment of such chronic lung disease that follows a viral infection. This body of work supports a building body of evidence that suggests a target of effective therapy is related to pulmonary neutrophils.

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