Tracheo-bronchitis Associated with Crohn’s Disease
Improved on Inhaled Corticotherapy

Shin-ichi KINEBUCHI, Kazumasa OOHASHI, Toshinori TAKADA, Hiroshi MORIYAMA,
Hirohisa YOSHIZAWA, Osamu KOBAYASHI*, Eiichi SUZUKI** and Fumitake GEJYO

Abstract

We report a case of tracheo-bronchitis in Crohn’s disease. A 23-year-old Japanese woman who had been diagnosed with Crohn’s disease three years previously was hospitalized. She had been suffering from dry cough for one month. Computed tomography of the chest revealed marked thickening of the tracheal wall. Bronchoscopy showed erythematous and edematous mucosa with diffuse whitish granular lesions in the trachea and bronchi. The bronchial biopsy specimens showed non-specific inflammatory infiltrates consisting of lymphocytes and plasma cells, and hyperplasia of bronchial glands. Inhaled corticotherapy, fluticasone propionate 800 µg/day, was effective for both the inflammatory mucosa and thickened tracheal wall.

Case Report

A 23-year-old Japanese woman with CD, who had been treated with nutrition therapy and mesalazine since 1999 at Niigata Prefectural Central Hospital, was admitted to our hospital in August 2002 for evaluation of dry cough since July 2002. She did not have any past history of bronchial asthma.

On admission, blood pressure was 92/64 mmHg, pulse rate was 80/min, and temperature was 37.2°C. Physical examination was negative except for mild abdominal tenderness. Laboratory data showed a normal white blood cell count, hemoglobin 10.1 g/dl, erythrocyte sedimentation rate 57 mm/h, and C-reactive protein 5.9 mg/dl. The serum protein was normal. The anti-nuclear antibodies, anti-dsDNA antibodies, and biological false positive serological tests for syphilis were present. Perinuclear and cytoplasmic anti-neutrophil cytoplasmic antibodies (MPO-ANCA and PR3-ANCA) were absent. Serological tests for Mycoplasma pneumoniae by the complement fixation method and for Chlamidia pneumoniae by ELISA were positive. Arterial blood gas values on room air were normal. Pulmonary function tests showed a decreased forced expiratory volume in one second (FEV1) and an upper airway obstructive pattern on flow-volume curve. Sputum culture was negative, including Mycobacteria.

Chest radiograph showed stenosis of the upper trachea compared with that taken nine months before admission (Fig. 1A), but there were normal findings in both lung fields (Fig. 1B). Computed tomography (CT) of the chest revealed a marked increase in tracheal wall thickness and stenosis of the sub-glottic trachea without mediastinal lymph node enlargement (Fig. 1C, D). Bronchoscopy disclosed erythematous and edematous mucosa of the trachea and main bronchi with diffuse whitish granular lesions and disappearance of the

From the Division of Respiratory Medicine, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, *the Department of Respiratory Medicine, Niigata Prefectural Central Hospital, Joetsu and **the Department of General Medicine, Niigata University Medical and Dental Hospital, Niigata

Received for publication November 5, 2003; Accepted for publication April 26, 2004

Reprint requests should be addressed to Dr. Toshinori Takada, the Division of Respiratory Medicine, Graduate School of Medical and Dental Sciences, Niigata University, 1-757 Asahimachi-dori, Niigata 951-8510
stripes of tracheal cartilage and longitudinal mucosal folds on the membranous portion of the tracheal wall (Fig. 2). Especially, there was a severe stenosis of the sub-glottic trachea with mucosal inflammation. Bronchial mucosa taken from the spur between the right upper bronchus and intermediate trunk showed non-specific chronic inflammatory infiltrates with mononuclear cells consisting of lymphocytes and plasma cells and hyperplasia of bronchial glands, without non-caseating tuberculoid granuloma (Fig. 3).

The patient was initially treated with codeine phosphate on admission, so that the dry cough was gradually relieved. Inhaled steroids (fluticasone propionate 800 μg/day) were prescribed to treat the mucosal inflammation of trachea and bronchi. After two weeks with inhaled corticotherapy, bronchoscopy showed reappearance of the stripes of tracheal cartilage and longitudinal mucosal folds with little whitish granular lesions (Fig. 4A, B). Under inhaled steroids, dry cough did not relapse when codeine phosphate was withdrawn. The stenosis of the upper trachea on chest radiograph was improved at the time of discharge (Fig. 4C). Pulmonary function tests showed an improvement in FEV1, but an upper airway obstructive pattern in the flow-volume curve was still present (Fig. 5). A follow-up CT after 3 months with inhaled corticotherapy showed an almost normal thickness of the tracheal wall (Fig. 4D). Inhaled steroids were reduced to 400 μg/day, without relapse of respiratory symptoms, thereafter.

**Discussion**

We report the case of a young Japanese woman with CD who developed tracheo-bronchial inflammation and stenosis, and had a dramatic response to inhaled corticotherapy. Since Kraft et al described bronchopulmonary disease with IBD in 1976 (2), there have been several reports of tracheobronchial involvement as an uncommon complication of CD. In previous reports, the patients were mainly young women.
and usually had respiratory symptoms of cough and dyspnea, rarely with acute respiratory failure leading to mechanical ventilation (5). Upper airway obstruction was sometimes found and pulmonary function tests showed an obstructive respiratory disorder in those patients (5, 7).

Mucosal inflammation with a whitish granular lesion, which appears to be similar to cobblestone appearance in colonoscopy, is a characteristic endobronchial finding in former reports (4–7). Histopathological findings of bronchial biopsy generally show mucosal and submucosal infiltrates of various inflammatory cells such as lymphocytes, plasma cells, macrophages and neutrophils (4–7), as seen in the present patient. Those endoscopic and histopathological findings suggest that the inflammation of tracheo-bronchial mucosa may be produced by a mechanism of mucosal inflammation similar to that of the colon, associated with activations of T-cell lymphocyte and macrophage (8). The possibility exists that common pathogenic antigens might be present in both colonic and tracheo-bronchial mucosa and bring about mucosal immune response. Tracheo-bronchitis developed without deterioration of CD in the present case. Although the trigger of the immune response may be essentially the same between the respiratory tract and large intestine, amplification of the inflammatory process might be different, resulting in unparalleled clinical courses between those organs. Tracheo-bronchitis might have developed by bronchial asthma and infectious diseases such as Mycoplasma or Chlamidia infection, but her clinical history and pathological findings did not suggest the possibility of asthma. Although serological tests for Mycoplasma

Figure 2. Bronchoscopy showing erythematous and edematous tracheal mucosa with diffuse whitish granular lesions and disappearance of the stripes of tracheal cartilage at the trachea (A), carine (B), left main bronchus (C), and first division of the left main bronchus (D).
Figure 3. Bronchial biopsy: bronchial mucosa shows non-specific chronic inflammatory infiltrates and hyperplasia of bronchial glands [HE stain, ×10 (A)]. Most of the inflammatory infiltrates were lymphocytes and plasma cells [HE stain, ×40 (B)]. Non-caseating tuberculoid granuloma and eosinophils were not found in the specimen.

Figure 4. Improvement of tracheobronchitis with inhaled corticotherapy. Bronchoscopy after two weeks with inhaled corticotherapy showing reappearance of the stripes of tracheal cartilage with little whitish granular lesions at the trachea (A) and carina (B). Chest radiograph at the time of discharge (C) and chest CT after three months (D) with inhaled corticotherapy showing almost normal thickness of the tracheal wall.
pneumoniae and Chlamidia pneumoniae were positive, respiratory infection may not be a major cause in this case because tracheo-bronchitis improved by inhaled steroids only without antibiotics against these organisms.

Cases of CD with systemic lupus erythematosus (SLE) have been described in several reports (9, 10). ANCA were also often positive in patients with IBD (11). These findings indicate that CD is associated with auto-immune disorder. The anti-nuclear antibodies, anti-dsDNA antibodies, and biological false-positive serological tests for syphilis were present in the present patient. Other symptoms and/or laboratory findings of SLE are absent now, but our patient may be diagnosed with SLE in the future.

Tracheo-bronchial involvement in CD histologically demonstrates dense submucosal infiltrates consisting of lymphocytes and plasma cells in the trachea and main bronchi and it typically responds to steroids symptomatically in bronchoscopic findings and pulmonary function tests. Two previous cases initially received a moderate to high dose of oral steroids followed by inhaled steroids; fluticasone 1,000 μg and budesonide 1,600 μg (5, 7). In one case, a moderate dose of prednisone at 20 mg daily was not effective, and was increased to 60 mg daily (4). In the other case, tracheo-bronchial involvements developed despite high-dose inhaled steroids (beclomethasone 1,500 μg) (6). The present patient received inhaled steroid as an initial therapy and respiratory involvement improved markedly without oral corticosteroid. The localization of respiratory involvement and histological findings of the present case were similar to those of the previous cases. Although the reason for differences in therapy responses is still unclear, tissue destruction and amplification of the inflammatory response in tracheo-bronchial mucosa might be so heterogeneous that the effect of inhaled steroids differed case by case.

Inhaled corticosteroids are the cornerstone of treatment for asthma. Asthma is now defined as a type-2 helper T-cell (Th2) -mediated inflammatory disease involving both large and small airways (12). On the other hand, in CD, cytokine balance within the mucosa fails when antigen-presenting cells with bacteria generate mainly interleukin-12, thereby driving a Th1 response (8). Inhaled steroids may suppress Th1 type cytokines including interferon-γ and tumor necrosis factor-α produced by activated T-cells and macrophages in tracheo-bronchitis associated with CD correcting an imbalance between Th1 cells and Th2 cells in a reverse way to bronchial asthma.

Conclusion

We report a case of tracheo-bronchitis in CD with an excellent response to inhaled corticotherapy without oral steroids. An adequate dose of inhaled steroids can be an option for the initial treatment for tracheo-bronchitis in CD, even for cases with progressed tracheo-bronchial involvement.

References
2) Kraft SC, Earle RH, Roesler M, Esterly JR. Unexplained broncho-