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Severe airflow obstruction in a patient with ulcerative colitis and toxic epidermal necrolysis: A case report

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Abstract. Bronchiolitis is a rare condition mainly affecting the intralobular conducting and transitional small airways. The present study describes a case of severe airflow limitation in a patient with ulcerative colitis who developed toxic epidermal necrolysis following mesalazine therapy. Forced expiratory volume in one second was decreased and a flow-volume curve showed airflow limitation, but the single-breath diffusing capacity of the lung for carbon monoxide (DL_{CO}) and DL_{CO} divided by alveolar volume (DL_{CO}/VA) were not decreased. This rare clinical condition should be considered as a differential diagnosis for subjects presenting with sub-acutely developed airflow obstruction if the findings in chest computed tomography scans demonstrate hyperinflation but few low-attenuation areas. Relatively well-preserved DL_{CO} and DL_{CO}/VA provide a clue to establishing the correct diagnosis.

Introduction

Obstructive bronchiolitis (OB) is a rare disease and affects small airways of the lung and is associated with restriction of the airways (1). OB must be considered as a potential diagnosis in patients with obstructive respiratory impairment, the most common symptom of which is dyspnea (1). This inflammatory process is associated with various conditions, including ulcerative colitis (UC) and toxic epidermal necrolysis (TEN). UC is a chronic relapsing inflammatory bowel disease of uncertain etiology. UC may occur at any age, but is most commonly diagnosed in late adolescence or early adulthood (2). The incidence of UC has increased worldwide over recent decades, particularly in developing nations (2). Typical

symptoms of UC include, bloody diarrhea, abdominal pain, urinary urgency and tenesmus (2). TEN is acute drug-induced condition associated with severe blistering, skin peeling and multi-organ damage, and is classed in the same spectrum of diseases as Stevens-Johnson syndrome (3,4). TEN symptoms typically resemble severe scalding, with $\geq 30\%$ top layer of skin detaching from the lower dermis (3). OB must be considered as a differential diagnosis in patients with obstructive respiratory impairment (4). In the case reported in the present study a patient with ulcerative colitis (UC), who developed toxic epidermal necrolysis (TEN) (5) following mesalazine therapy, presented with severe airflow limitation.

Case report

A 53-year-old male was received at the Mito Medical Center (Mito, Japan) with a two-month history of exertional dyspnea, which was not accompanied by a dry cough, fever, chill or chest pain. There was no history of antecedent respiratory tract infection. The patient had a 15-pack-year smoking history, having stopped 20 years previously, and no allergies. There was no recognized history of exposure to fumes or mineral dusts. The patient had been diagnosed as having UC 25 years previously and was given mesalazine therapy, since therapy with prednisolone had not led to any improvement in the UC. Following an increase in the dose of mesalazine to 2,250 mg/day, the patient developed a high fever ($>38^{\circ}\text{C}$) and a large number of red papules and erythemas. The eruptions rapidly spread to the whole body and changed to erythroderma in one week. The eruptions additionally caused blistering, epidermolysis and erosion of $>10\%$ of the body's surfaces a few days later. No findings suggested staphylococcal scalded skin syndrome. Based on the skin symptoms and clinical course, the patient was diagnosed with TEN due to the mesalazine. The patient received several courses of steroid pulse therapy with methylprednisolone and plasma exchange therapy. The patient recovered from the TEN as a result of these intensive therapies, although scars and pigmentation in the trunk and extremities remained. Informed consent was obtained from the patient.

On admission, the respiratory rate of the patient was 18 beats/min and his breath sound was diminished, without any expiratory rhonchi. Clubbing was absent. The forced

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Key words: airflow obstruction, ulcerative colitis, mesalazine, toxic epidermal necrolysis, obstructive bronchiolitis

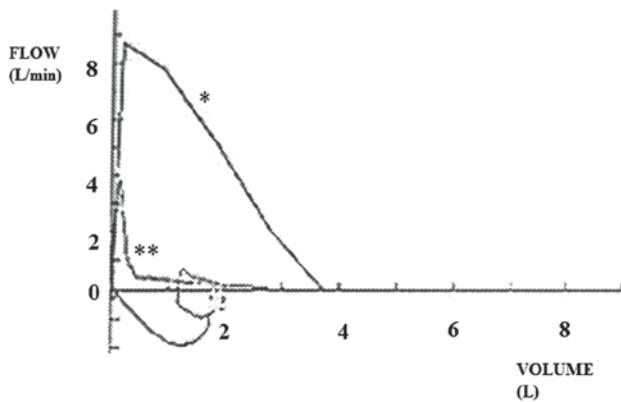


Figure 1. Flow-volume curve at the time of presentation to the hospital with dyspnea on effort. *Predicted curve; **measured curve.

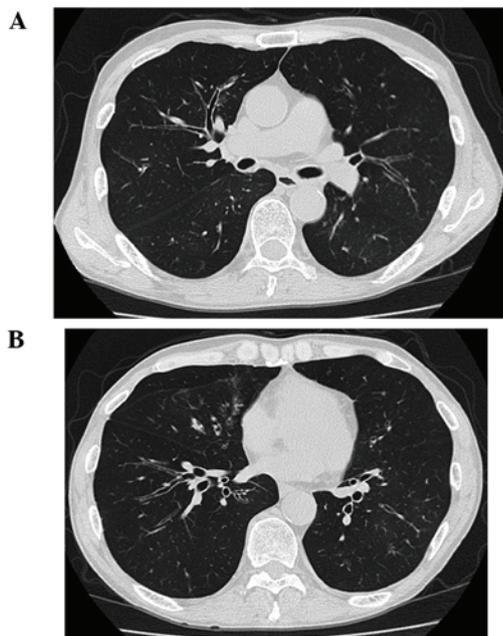


Figure 2. Slices (A) and (B) of chest computed tomography scan display bronchiectasis and thickening of the walls of the central bronchi in both lungs.

expiratory volume in one second ($FEV_{1,0}$) was 0.77 liters (36.4% of predicted) and the forced vital capacity was 2.97 liters (80.1% of predicted). A flow-volume curve showed airflow limitation (Fig. 1). The residual volume was 2.57 liters (153% of predicted), the functional residual capacity was 3.97 liters (97% of predicted) and the single-breath diffusing capacity of the lung for carbon monoxide (DL_{CO}) and DL_{CO} divided by alveolar volume (DL_{CO}/VA) were 105 and 93% of the predicted values, respectively. A chest radiograph showed scarce hyperinflation. No improvement in the $FEV_{1,0}$ was observed following inhalation of a β -stimulant. A chest computed tomography (CT) scan showed only a small number of low-attenuation areas and bullae and demonstrated central bronchiectasis and a mosaic pattern, which intensified on expiration (Fig. 2). These findings were not consistent with pulmonary emphysema as a cause of severe airflow limitation. The results, including a respiratory function test and radiological examination, were highly suggestive of OB. Inhalation

of corticosteroid and anticholinergic agents, oral theophylline and inhaled corticosteroid were not effective in this patient. Respiratory rehabilitation and long-acting β_2 -agonist/inhaled corticosteroid appeared to cause a slight reduction in his exertional dyspnea; however, the potential role of these therapies requires further examination. The patient did not recover completely. Twenty-six months following disease onset the patient remained alive and was discharged from the outpatient clinic.

Discussion

OB is an inflammatory process that primarily affects small conducting airways of the lungs, resulting in differing levels of airflow limitation (2). This inflammatory process is associated with numerous conditions, including UC (5-7), bullous skin disease (8), Stevens-Johnson syndrome (9-14), graft versus host disease following a lung or bone marrow transplant (15-18) and certain drugs (1,6). The current patient was a middle-aged ex-smoker who complained of sub-acutely developed exertional dyspnea. Early-onset chronic obstructive pulmonary disease was initially suspected from the patient's symptoms and severe irreversible airflow limitation; however, the chest CT scan was not consistent with smoking-induced centrilobular emphysema in this case, although the diagnosis of panlobular emphysema could not be refuted. It is generally accepted that decreases in DL_{CO} and DL_{CO}/VA are useful indicators of pulmonary emphysema (19,20); therefore, these parameters were evaluated, but no decreases were found despite severe irreversible airflow limitation. A mosaic pattern and bronchiectasis have been reported to be the typical findings in OB, although there have been cases demonstrating only diffuse hyperinflation, bronchial wall thickening and bronchiectasis, or even normal findings on a CT scan (21,22). In the present patient, a chest CT scan showed bronchiectasis and thickening of the walls of the central bronchi in both lungs.

In the present case, the patient had UC and had received plasma exchange for the treatment of TEN, which are known causes of OB (1,4-6,23). TEN and Stevens-Johnson syndrome are defined as drug-related dermatopathies on the same spectrum (4), and a case of severe OB associated with TEN has been previously reported (24). We speculated that the OB in the present case may have developed as a result of an impairment of the respiratory mucous membrane, as observed in Stevens-Johnson syndrome, and that there was a high probability that this severe airflow limitation had an association with the development of TEN due to mesalazine therapy. Thus, if drugs were directly responsible for the development of OB in this patient, mesalazine would be a highly probable candidate.

Regarding adverse events due to mesalazine, certain pulmonary toxicities have already been reported (5,6,25). Notably, two previous reports have described OB in patients with UC receiving mesalazine (6,7), as observed in the present case; however, the cause and precise mechanism of OB resulting from mesalazine treatment is not currently known.

Pathological examination of the affected bronchioles is important to the diagnosis of OB (1,26). The narrowing of

bronchioles by necrotic and fibrotic changes are the main pathogenesis of OB (1,26); however, the majority of the patients with OB have exertional dyspnea with airflow limitation and it may, therefore, be challenging to obtain sufficient specimens from these individuals. The present patient declined a surgical approach, and the lung specimen could not be obtained.

In conclusion, the present study describes a case of OB in a patient with UC who developed TEN following mesalazine therapy. This rare clinical combination should be considered as a differential diagnosis, even for middle-aged, ex-smoking subjects presenting with sub-acute developed airflow obstruction, if the findings in the chest CT scan demonstrate hyperinflation but few low-attenuation areas. Relatively well-preserved DL_{CO} and DL_{CO}/VA can provide a clue to establishing a correct diagnosis.

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