◎症 例

A case with persistent asthma symptoms despite fluticasone treatment in which concomitant treatment with montelukast and perilla seed oil-rich supplementation significantly improved asthma control

Shingo Takata[1)], Kozo Ashida[1)], Yasuhiro Hosaki[1)], Masanori Hamada[2)], Naofumi Iwagaki[1)], Hiroshi Kikuchi[1)] and Fumihiro Mitsunobu[1)]

[1)]Division of Medicine, [2)]Division of Rehabilitation, Misasa Medical Center, Okayama University Hospital of Medicine and Dentistry

Abstract：A 25-year-old woman had the chief complaint of recurrent episodes of dyspnea and wheeze. Asthma had been diagnosed at infant years and sometimes experienced asthma attacks. She graduated senior high school and entered technical school in Tokyo. She received fluticasone (400μg daily) but exacerbation continued after she became an office clerk. She returned Kurashiki in October 2001 but had wheeze and asthma exacerbations. She was admitted to our hospital for evaluation and treatment of bronchial asthma on August 2, 2002. After admission, her symptoms subsided within some days. She was treated with montelukast and perilla seed oil-rich supplementation. The number of eosinophils decreased, decrease was observed in leukotriene (LT) B4 generation and in LTC4 generation, and pulmonary function improved following montelukast and perilla seed oil-rich supplementation for 4 weeks. The patient had no exacerbation under treatment and was discharged from the hospital on September 2, 2002. For some patients with persistent asthma, inhaled corticosteroids may fail to achieve adequate control possibly because corticosteroids do not completely inhibit the synthesis and release of cysteinyl leukotrienes (cysLTs) in the lung. Montelukast blocks the interaction of cysLTs with their receptor and resulting downstream events and perilla seed oil-rich diet suppresses LT generation. Combination therapy with montelukast and perilla seed oil-rich diet is more effective than montelukast or perilla seed oil-rich diet alone because of additive effects of montelukast with perilla seed oil-rich diet. We suggest that montelukast and perilla seed oil-rich supplementation are effective options when bronchial asthma patients receive inhaled corticosteroid but exacerbation continues.

Key words：montelukast, bronchial asthma, leukotriene C4, perilla seed oil-rich supplementation, fluticasone

Introduction

Asthma is a chronic inflammatory disease characterized by the presence of inflammatory cells such as T lymphocytes, mast cells, and eosinophils in the airways[1]. Characteristic features of asthma include mucus hypersecretion, airways hyperreactivity, and changes in airway morphology (for example, increased airway smooth muscle mass, subepithelial fibrosis, edema, eptithelial cell damage). Cysteinyl leukotrienes (cysLTs) such as leukotriene (LT) C_4, LTD_4, and LTE_4 are produced from a variety of inflammatory cells including mast cells, basophils, eosinophils and macrophages, all of which may contribute to the pathogenesis of asthma[2-5]. Antileukotriene drugs are the effective therapy for asthma currently available and have been used in such patients with few side effects[1,6]. Previously, we have reported the inhibitory effect on the generation of leukotrienes by peripheral leucocytes with a diet containing perilla seed oil, a vegetable oil rich in α-linolenic acid (α-LNA)[7]. However, it is still unclear whether concomitant treatment with montelukast and dietary supplementation of perilla seed oil influences on the pathophysiology of bronchial asthma or not. We report a case with mild airway obstruction and persistent asthma symptoms despite fluticasone treatment in which concomitant treatment with montelukast and perilla seed oil-rich supplementation significantly improved asthma control.

Case Report

A 25-year-old woman had the chief complaint of recurrent episodes of dyspnea and wheeze. She had a history of pneumonia in childhood and allergic rhinitis. She was an office clerk. She drank alcohol socially and did not use tobacco. Her mother had hypertension and migraine. Her father's brother had bronchial asthma. Her mother's brother had lung cancer. Two brothers had atopic dermatitis.

Asthma had been diagnosed at infant years and she was often admitted to hospitals until she graduated elementary school. She sometimes experienced asthma attacks in junior and senior high school. She graduated senior high school and entered technical school in Tokyo. She received fluticasone (400 μg daily) but exacerbation continued after she became an office clerk. She returned Kurashiki in October 2001 but had wheeze and asthma exacerbations. She was admitted to our hospital for evaluation and treatment of bronchial asthma on August 2, 2002.

Her height was 161.2cm and body weight was 62.7kg; her body temperature was 36.8℃, blood pressure 90/60mmHg and heart rate 68/minute. There were no rales in the lung field. Heart sounds were normal. The laboratory findings on admission are shown in Table 1. Leukocyte count was 4600/μℓ with 37% polymorphonuclear cells, 13% eosinophils (an absolute count of 598/μℓ), 49% lymphocytes and 1% monocytes. Immunoglobulin E was elevated 1253 IU/ml. Radioallergosorbent tests for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, house dust, cedar, cat and dog were positive.

Table 1 Laboratory data on admission

CBC		Allergic examination	
WBC	4600/μℓ	IgE(RIST)	1253 IU/ml
Stab	0.0%		
Seg	37.0%	IgE(RAST)	
Lymph	49.0%	*Dermatophagoides pteronyssinus*	
Mono	1.0%	*Dermatophagoides farinae*	
Eos	13.0%	House dust 1	
Baso	0.0%	House dust 2	
RBC	434×10⁴/μℓ	*Aspergillus*	
Hgb	13.0 g/dℓ	*Candida*	
Hct	38.1%	Cedar	
PLT	23.1×10⁴/μℓ	Cat (dandruff)	
		Rice	
Chemistry		Cockroach	
T.P.	7.3 g/dℓ	Dog (dandruff)	
Alb	4.0 g/dℓ	Serology	
BUN	7.3 mg/dℓ	IgG	1301 mg/dℓ
Cr	0.7 mg/dℓ	IgA	256 mg/dℓ
UA	5.2 mg/dℓ	IgM	134 mg/dℓ
AST	18 IU/ml	HBs Ag	(-)
ALT	25 IU/ml	Anti-HCV Ab	(-)
ChE	11.49 IU/ml		
γ-GTP	9 IU/ml	Hormone study	
AMY	51 IU/ml	Cortisol	23.4 μg/dℓ
T.Chol	158 mg/dℓ		
TG	85 mg/dℓ		
HDL	64 mg/dℓ		

After admission, her symptoms subsided within some days(Fig. 1). Fluticasone(400 μg daily) was stopped and budesonide(400 μg daily) was given.

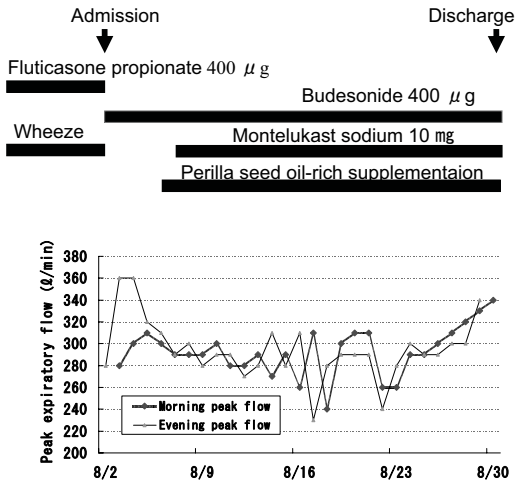

Fig.1 Clinical course

She was treated with montelukast and perilla seed oil-rich supplementation. The number of eosinophils decreased following montelukast and perilla seed oil-rich supplementation for 4 weeks (598 to 405/μℓ) (Fig. 2). Decrease was observed in LTB4 generation (94.2 to 60.0ng/5×10^6 cells) (Fig. 3) and in LTC4 generation by leucocytes (76.5 to 49.4ng/5×10^6cells) (Fig. 4) for 4 weeks. Pulmonary function tests were performed using a Chestac 33 (Chest Co., Tokyo, Japan) linked to a computer. Vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), forced expiratory flow after 25% of expired FVC (FEF_{25}), forced expiratory flow after 50% of expired FVC (FEF_{50}), forced expiratory flow after 75% of expired FVC (FEF_{75}), mean expiratory flow during the middle half of the FVC (FEF_{25-75}) and peak expiratory flow (PEF) improved at 4 weeks after receiving montelukast and dietary supplementation with perilla seed oil (Table 2). Morning PEF and evening PEF increased 60.0 ℓ/min for 4 weeks (Fig. 1). The patient had no exacerbation under treatment and was discharged from the hospital on September 2, 2002.

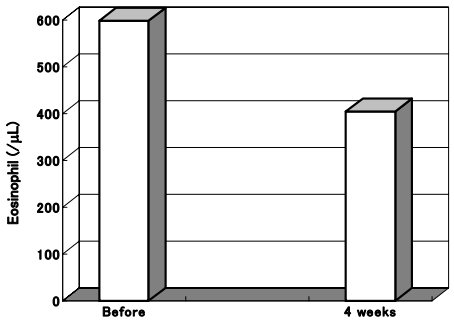

Fig.2 Changes in the number of eosinophils.
The number of eosinophils decreased for 4 weeks.

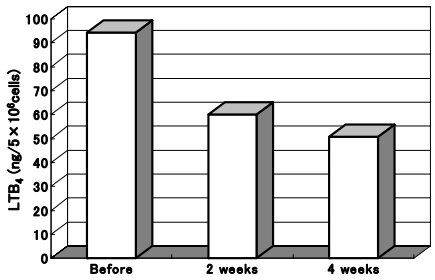

Fig.3 Changes in LTB_4 generation by leucocytes
LTB_4 generation decreased after montelukast and perilla seed oil-rich supplementation for 2 and 4 weeks.
LTB_4:leukotriene B_4

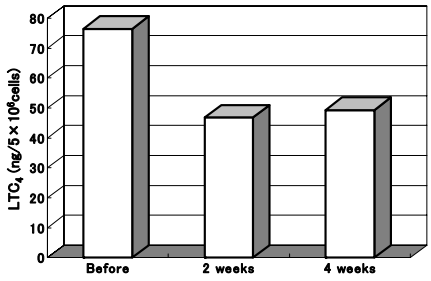

Fig.4 Changes in LTC_4 generation by leucocytes
LTC_4 generation decreased after montelukast and perilla seed oil-rich supplementation for 2 and 4 weeks.
LTC_4:leukotriene C_4

Table 2 Changes of ventilatory parameters by montelukast and dietary supplementation

	Montelukast and dietary supplementation	
	Before	4weeks
VC(ℓ)	3.32	3.49
FVC(ℓ)	3.32	3.40
FEV_1(ℓ)	2.44	2.93
FEF_{75}(ℓ/sec)	3.71	6.02
FEF_{50}(ℓ/sec)	2.38	4.09
FEF_{25}(ℓ/sec)	0.53	1.41
FEF_{25-75}(ℓ/sec)	2.29	3.98
%RV(%)	72.3	41.9
%FRC(%)	98.6	88.7
%PEF(%)	57.3	93.2
%DLco(%)	85.3	94.0

VC:vital capacity, FVC:forced vital capacity
FEV_1: forced expiratory volume in one second
FEF_{75}: forced expiratory flow after 75% of expired FVC
FEF_{50}: forced expiratory flow after 50% of expired FVC
FEF_{25}: forced expiratory flow after 25% of expired FVC
FEF_{25-75}: mean expiratory flow during the middle half of FVC
RV: residual volume, FRC: functional residual capacity
PEF: peak expiratory flow, DLco: diffusing capacity for carbon monoxide

Discussion

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment[1]. Inhaled corticosteroids (ICS) affect a variety of inflammatory pathways in asthma and represent a gold standard in anti-inflammatory treatment[1]. However, for some patients with persistent asthma, ICS may fail to achieve adequate control possibly because corticosteroids do not completely inhibit the synthesis and release of cysLTs in the lung[8]. The cysLTs induce many of the pathophysiological changes present in the lungs of patients with asthma, including airflow obstruction, mucus secretion, reduced mucociliary clearance, and inflammatory cell infiltration. Montelukast, a cysteinyl leukotriene type 1 (CysLT1) receptor antagonist, has been found to reduce airway eosinophilic inflammation in patients with chronic asthma[9-11]. Many inflammatory processes escape modulation by glucocorticosteroids, whereas glucocorticosteroids have paradoxical effects on other processes. Notable among these is the leukotriene pathway. Several clinical trials indicate an additive effect of glucocorticosteroids and montelukast on pulmonary function, even in patients receiving high-dose inhaled or oral glucocorticosteroids, suggesting that LT synthesis in asthmatic persons is resistant to glucocorticosteroids suppression[8]. For patients with persistent asthma symptoms

despite ICS treatment, concomitant treatment with montelukast significantly improves asthma control[10].

We have reported the inhibitory effect on the generation of LTs by peripheral leucocytes with a diet containing perilla seed oil, a vegetable oil rich in α-linolenic acid (α-LNA)[7]. Polyunsaturated fatty acids (PUFAs) of the n-3 fatty acids [EPA and docosahexaenoic acid (DHA)] suppress the production of '4-series' LTs by competitive antagonistic metabolism, which occurs at the level of LT hydrolase through the 5-lipoxygenase pathway. Therefore, PUFAs may potentially alter LT generation by leucocytes[12]. Several reports have shown the beneficial effects of EPA or fish oil on bronchial asthma[13-17]. However, little is known about the effects of adding montelukast combined with dietary supplementation of perilla seed oil on asthma.

This case had mild airway obstruction and persistent asthma symptoms despite ICS treatment in which the addition of montelukast and perilla seed oil-rich supplementation produced substantial improvements in asthma control. Reiss reported that montelukast significantly improved airway obstruction, as shown by an increase in FEV_1 of 13.1%, in morning PEF of 24.0 ℓ/min, and in evening PEF of 15.9 ℓ/min in asthmatic patients[18]. Okamoto et al. reported that perilla seed oil-rich supplementation was effective in the treatment of asthma, as shown by an increase in FEV_1 of 11.7% and in morning PEF of 40.7 ℓ/min[19]. In this case montelukast and perilla seed oil-rich supplementation significantly improved pulmonary function, as shown by an increase in FEV_1 of 20.1%, in morning PEF of 60.0 ℓ/min, and in evening PEF of 60.0 ℓ/min in asthmatic patients. Montelukast blocks the interaction of cysLTs with their receptor and resulting downstream events[18] and perilla seed oil-rich diet suppresses LT generation[19]. Combination therapy with montelukast and perilla seed oil-rich diet is more effective than montelukast or perilla seed oil-rich diet alone because of additive effects of montelukast with perilla seed oil-rich diet. We suggest that montelukast and perilla seed oil-rich supplementation are effective options when bronchial asthma patients receive ICS but exacerbation continues.

ACKNOWLEDGEMENTS

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Fluticasone 投与にもかかわらず症状が軽快せずn-3系不飽和脂肪酸強化食による食事療法及びモンテルカストが著効した気管支喘息の１例

高田真吾[1)]，芦田耕三[1)]，保﨑泰弘[1)]，
濱田全紀[2)]，岩垣尚史[1)]，菊池　宏[1)]，
光延文裕[1)]

岡山大学病院三朝医療センター内科[1)]
同　三朝医療センターリハビリテーション科[2)]

症例は25歳女性，主訴は呼吸困難，喘鳴。乳児期気管支喘息発症し，以後も喘息発作を認めた。高校卒業後上京し，就職後fluticasone propionate 400μg投与にもかかわらず，喘息発作が続いていた。2001年10月倉敷に帰郷後も喘鳴，発作を認め，2002年８月２日精査加療目的で当院入院となった。入院後速やかに喘鳴は消退した。エゴマ油食，montelukast sodium投与開始し，血中好酸球，白血球leukotriene B4，leukotriene C4低下，呼吸機能改善を認めた。その後喘息発作，喘鳴などは再発せず，９月２日退院となった。吸入ステロイド薬単独治療では症状を十分に管理できない患者が存在する。その原因としてステロイド薬はロイコトリエンの産生を完全に抑制できないことが挙げられる。ロイコトリエンによる気道炎症は，montelukastをはじめとするロイコトリエン受容体拮抗薬によって特異的に抑制され，エゴマ油食もロイコトリエン産生を抑制すると報告されている。本症例ではmontelukastおよびエゴマ油食の相加効果により，各々の単独投与より良好な結果が得られた。従って吸入ステロイドで喘息コントロール不良な症例に対してmontelukastおよびエゴマ油食を併用することが望まれる。

索引用語：モンテルカスト，気管支喘息，ロイコトリエンC4，エゴマ油食，フルチカゾン