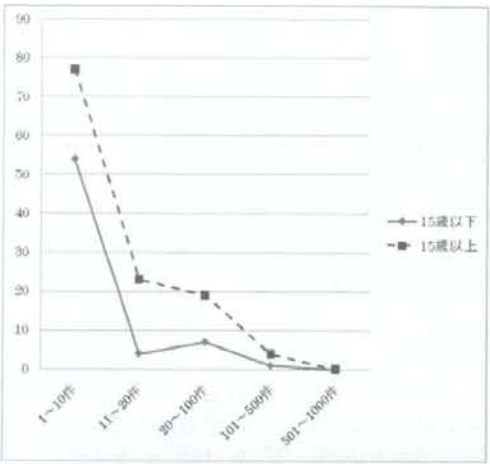

図１　吸入ステロイド薬処方件数分布
横軸　ステロイド処方件数
縦軸　薬局数

小児ばかりでなく、成人でもロイコトリエン拮抗薬の処方件数が平均 28 件（0 件から 1000 件）と吸入ステロイド薬の処方件数を上回った。喘息予防管理のガイドラインは 79%の認知度であり、製薬会社のパンフレットや研究会による情報が多かった。ただし、月 20 件以上の吸入ステロイド処方をしている薬局についても認知度は 84%に留まった。また、ガイドラインの冊子が薬局に置いてある施設は 25%であった。遠隔教育の手段としては、現段階ではインターネットよりパンフレットが多く、Ｂ５からＡ４で５から 10 ページ程度という希望が最も多かった（図２）。

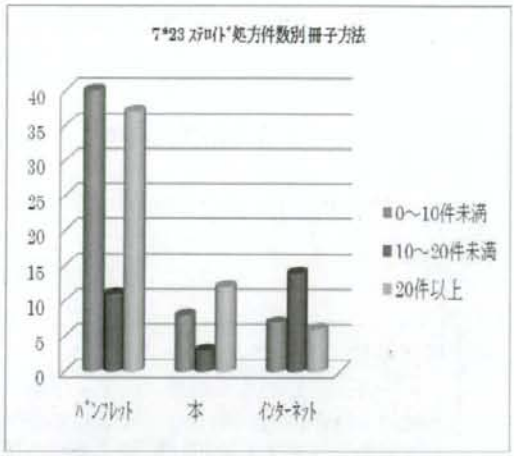

図２遠隔教育用の手段の希望
薬局のステロイド処方件数で層別化したものを示す。縦軸は薬局数

遠隔教育の内容としては、喘息病態・発症機序の他、妊娠時の喘息治療や遺伝的背景に関する要望が多かった。吸入ステロイド薬の服薬指導は初回のみが 64%を占めた（図３）。喘息治療およびアスピリン喘息の疑いに対する受診勧告件数は少なかった。

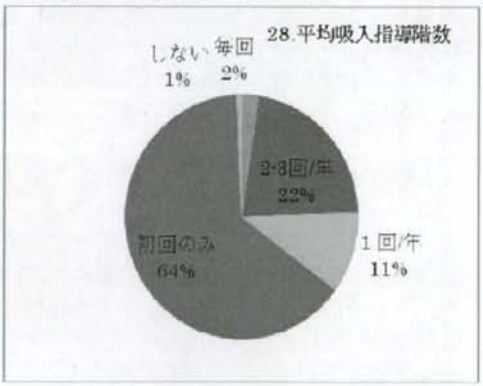

図３　吸入ステロイドの吸入指導回数

D．考察

喘息薬の処方箋件数は薬局によりばらつきが大きく、1000 件／月から 0 件に渡ったが、ガイドラインの認知度は処方のない薬局でも 76%と高水準を認めた。一方、100 件以上の処方があるにも関わらず存在を知らない場合が 10%以上認めたことは、普及活動時に留意すべき点と思われた。今後、開局薬局で、服薬指導のみならず、受診勧告がなされる事が期待されるが、まだその頻度はわず

かであることが示された。特に、遠隔教育の内容としては妊娠時の喘息時の薬物投与の仕方および発作予防に関するものが多く、この点について情報が不足している事が伺われた。

E. 結論

以前施行された、かかりつけ医に対するアンケートと同様、ガイドラインの認知度は高いものの、患者への指導には生かされるにはまだ不十分と考えられる。今後、調査結果を生かした遠隔教育システムを現場の薬剤師の協力のものと構築を勧めたい。

Ⅲ．研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
中川 秀己	スキンケア指導	五十嵐隆、専門編集：海老澤元宏	小児科臨床ピクシス：年代別アレルギー疾患への対応	中山書店	東京	2009	236-239

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kawahata K, Yamaguchi M, Kanda H, et al.	Severe airflow limitation in two patients with systemic lupus erythematosus: effect of inhalation of anticholinergics.	Mod Rheumatol	18	52-56	2008
Tokuda H, Sakai F, Yamada H, et al.	Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study.	Intern Med	47	915-23	2008
Hoshino K, Suzuki J, Yamauchi K, Inoue H.	.Psychological stress evaluation of patients with bronchial asthma based on the chromogranin a level in saliva.	J Asthma	45	596-9	2008
Yamauchi K, Tamura G, Akasaka T, Chiba T, Honda K, Kishi M, et al.	Analysis of the Comorbidity of Bronchial Asthma and Allergic Rhinitis by Questionnaire in 10,019 patients.	Allergol Int	58	55-61	2009

Ⅳ．研究成果の刊行物・印刷

Mod Rheumatol (2008) 18:52–56
DOI 10.1007/s10165-007-0002-3

CASE REPORT

Severe airflow limitation in two patients with systemic lupus erythematosus: effect of inhalation of anticholinergics

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Abstract Airway involvement clinically presenting as dyspnea and an obstructive ventilatory defect is a rare but clinically important complication in systemic lupus erythematosus (SLE), since the airway manifestation is often progressive and resistant to systemic immunosuppressive therapy. Here we report two SLE patients with slowly progressive airflow limitation, which was clinically thought to be bronchiolitis obliterans. Both patients showed obvious improvement after inhalation of anticholinergics was started. Because anticholinergics are highly safe and never immunosuppressive, inhalation of these drugs might be useful in the therapeutic strategies for airflow limitation accompanying SLE or other collagen diseases.

Keywords Airflow limitation · Anticholinergics · Bronchiolitis obliterans (BO) · Obstructive ventilatory defect · Systemic lupus erythematosus (SLE)

Introduction

Respiratory system involvement sometimes occurs in systemic lupus erythematosus (SLE). SLE patients presenting with uncontrollable lung abnormalities may need special clinical attention, since decreased pulmonary function greatly hampers the patients' activities of daily living. The airway is a relatively rare site of pulmonary complication in SLE. However, chronic progression of airflow limitation, for which a diagnosis of bronchiolitis obliterans (BO) is clinically suspected, has been generally recognized as a potentially life-threatening, difficult-to-treat complication in SLE, although its precise pathogenesis and incidence remain unclear [1, 2]. Here, we report two SLE patients with slowly progressive airflow limitation that showed obvious improvement after inhalation of anticholinergics was started.

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Case report

Case 1

A 42-year-old female complained of slowly progressive exertional dyspnea and showed severe airflow limitation at a follow-up visit to our outpatient clinic in January 2003.

At the age of 20, SLE was diagnosed on the basis of lymphocytopenia, proteinuria (lupus nephritis type V), anti-nuclear autoantibodies, anti-ds DNA antibodies (54 IU/mL) and hypocomplementemia, and corticosteroid treatment was started. At the age of 37, a pulmonary function test had revealed an obstructive abnormality, but without any complaint of dyspnea. Two years later, exertional dyspnea developed and gradually worsened. Although a β_2-agonist partially improved her FEV1 from 1.06 to 1.57 L, her dyspnea was not affected by further treatment with a long- or short-acting β_2-agonist, corticosteroid inhaler and oral theophylline, in addition to oral prednisolone at 10–17 mg daily plus cyclosporine A, azathioprine or mizoribine. At the age of 41, her FEV1 was 0.77 L. Her serum IgE level was 7 IU/mL, and neither IgE specific for house dust mites nor blood eosinophilia was detected.

In January 2003, her FEV1 declined to 0.56 L (Fig. 1a, b). The diffusing capacity was well preserved. A chest X-ray (Fig. 1c) demonstrated no obvious abnormalities in either lung field. Chest CT, taken in both the inspiratory and expiratory states, did not show air-trapping patterns, but it indicated mild thickening of the bronchial walls without bronchiectatic changes (Fig. 1e, f). Although she showed prolonged expiration, there were no episodes suggesting asthma, such as nocturnal attacks of wheeze or cough. She had never smoked. Association of rheumatoid arthritis and/or Sjögren's syndrome was ruled out. Inhalation of oxitropium bromide at a total daily dose of 600 μg was started, and her dyspnea was slightly alleviated in the evening of the first inhalation day. One month later, her dyspnea, initially rated as Hugh-Jones grade II or III, completely disappeared. Three months later, her flow-volume curve and FEV1 were obviously improved (Fig. 1a, b). Other anticholinergics, i.e., flutropium bromide and tiotropium bromide, were tried, and their clinical efficacy on her symptoms was similar to that of oxitropium. The patient said that her dyspnea returned when she forgot the inhalation for even 1 day. She has continued the oxitropium inhalation for the following 3 years and has experienced no respiratory symptoms. A chest X-ray taken during the course of this anticholinergic therapy (Fig. 1d) showed slight elevation of the bilateral diaphragm compared with the X-ray of Fig. 1c, suggesting that there had been mild air-trapping before the inhalation was started.

Case 2

A 66-year-old female was admitted to our hospital in September of 2005 with a complaint of slowly progressive exertional dyspnea.

At the age of 56, a diagnosis of SLE was made based on serositis, thrombocytopenia, lymphocytopenia, proteinuria, anti-ds DNA antibodies (12 IU/mL), antiphospholipid antibodies and hypocomplementemia, and corticosteroid treatment was started. Three years later, exertional dyspnea manifested and gradually worsened. Lung function studies revealed obvious obstructive changes, but the total lung capacity (TLC) and diffusing capacity were relatively preserved (Fig. 2a). She had never smoked. Although a β_2-agonist inhaler partially improved her FEV1 from 0.62 to 0.89 L, that treatment plus a corticosteroid inhaler showed little effect on her dyspnea. Her serum IgE level was 36 IU/mL. Neither IgE specific for house dust mites nor blood eosinophilia was detected.

A respiratory function test on admission showed a severe obstructive pattern, suggesting that airflow limitation was responsible for her slowly progressive symptoms (Fig. 2a, b). Association of rheumatoid arthritis and/or Sjögren syndrome was ruled out. Chest X-rays (Fig. 2c) showed no obvious abnormalities in either lung field except for a dull left-side costophrenic angle due to past splenectomy. A chest CT scan, taken in both the inspiratory and expiratory states, failed to show air-trapping patterns, although mild thickening of the bronchial walls was seen (Fig. 2e). There were no episodes of wheeze or attacks, suggesting that bronchial asthma was unlikely. Based on the clinical course of Case 1, we decided to try inhalation of an anticholinergic in this patient; tiotropium bromide was chosen because of its high affinity for M3 muscarinic receptor. Surprisingly, her dyspnea disappeared on the day of the first inhalation. One week later, her flow volume curve and FEV1 showed great improvement (Fig. 2a, b). Six months later, an airway response to β_2-agonist inhalation was not obvious (before inhaling: FVC 2.04 L, FEV1 0.86 L; after inhaling: FVC 2.09 L, FEV1 1.01 L). She has continued tiotropium inhalation for the following 12 months and has experienced no worsening of her respiratory symptoms. A chest X-ray taken during the course of this anticholinergic treatment (Fig. 2d) showed no changes, although her pulmonary function was greatly improved.

Discussion

Besides SLE, the patients described in this report did not have any other rheumatic diseases, such as Sjogren's syndrome or rheumatoid arthritis, because there were no findings of dry eye and dry mouth, arthritis, rheumatoid factor or anti-Ro/La autoantibodies. The key finding reported here is that both of the SLE patients who had presented with slowly progressive exertional dyspnea and an obstructive ventilatory defect demonstrated obvious improvement soon after inhalation of an anticholinergic was started. The clinical responses of the patients demonstrated that multiple agents belonging to the anticholinergics are effective, supporting the notion that their bronchodilating effects come from blockage of M3 receptors, thereby inducing antagonistic reduction of the vagal cholinergic tone of the airways [3]. Months to years of anticholinergic use successfully maintained the improved condition in both patients. No adverse events were observed. This is the first report of the effect of anticholinergics on the airway obstructive abnormality accompanying SLE.

SLE is a multisystem autoimmune disorder whose exact etiology remains unknown. Pulmonary involvement sometimes occurs in SLE, including acute or chronic interstitial pneumonitis, alveolar hemorrhage and bronchiolitis obliterans organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP) [2]. On the other

A

	11mo before	Start	3mo after	10mo after	2.5yr after
VC (L)	2.54	2.28	3.12	3.15	3.23
%VC	94	84	116	117	121
FEV1 (L)	0.77	0.56	1.00	1.04	1.16
FEV1%	30	25	32	33	36
PEFR (L/s)	1.33	1.18	2.10	2.72	2.20
V50 (L/s)	0.27	0.16	0.34	0.37	0.45
V25 (L/s)	0.11	0.09	0.11	0.10	0.13
TLC (L)	4.16	3.87		5.06	4.69
IRV (L)	0.99	0.75		1.34	1.30
TV (L)	0.44	0.45		0.44	0.45
ERV (L)	1.09	0.99		1.37	1.48
RV (L)	1.64	1.68		1.91	1.46
RV/TLC(%)	39.4	43.4		37.7	31.1
DLco	17.9	19.7		16.1	15.7
%DLco	94	104		86	80
DLco/VA	5.38	5.32		4.04	3.59

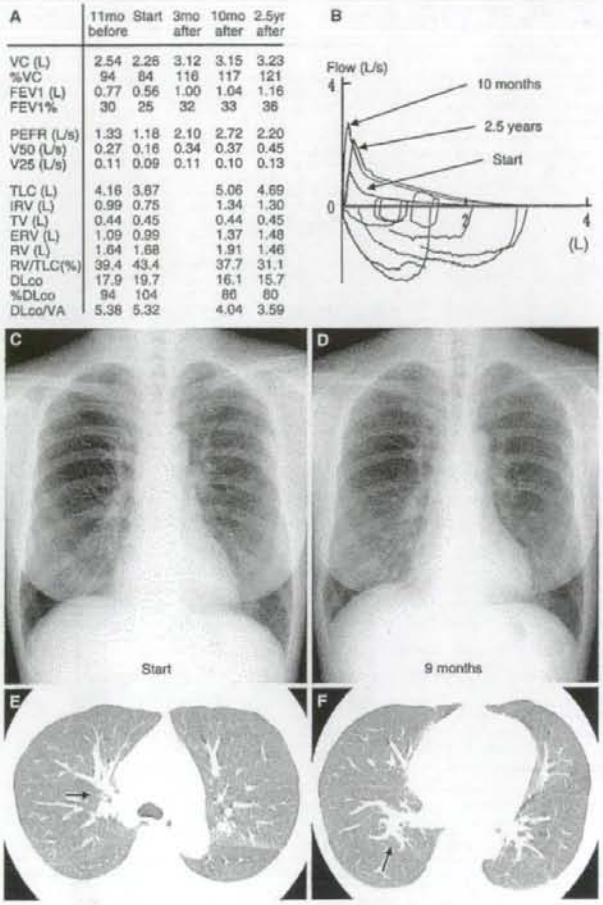
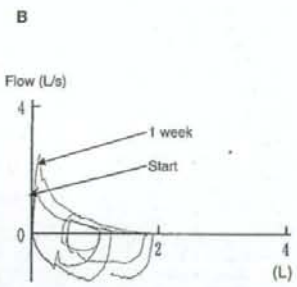


Fig. 1 a Results of pulmonary function tests in Case 1. The functional residual capacity was measured by the N_2 dilution method. Diffusion was assessed by the single-breath-holding method. *VC* vital capacity, *FEV1* forced expiratory volume in one second, *PEFR* peak expiratory flow rate, *TLC* total lung capacity, *IRV* inspiratory reserve volume, *TV* tidal volume, *ERV* expiratory reserve volume, *RV* residual volume, *VA* alveolar volume. b Flow volume curves just before ("start") and 10 months and 2.5 years after initiation of the anticholinergic inhalation therapy. c Chest X-ray taken before the inhalation was started. d Chest X-ray taken 9 months after anticholinergics inhalation was introduced. e, f Chest CT in the inspiratory state. *Arrows* indicate mildly thickened bronchial walls

hand, it is relatively rare for SLE to be accompanied by airflow limitation, and the available pathophysiological information is limited since lung biopsy is often contraindicated due to poor lung function in such patients. A small number of reports, in addition to autopsy studies, suggest that slowly progressive airflow limitation without lung parenchymal shadows may be due to a small-airway disorder called BO [4–6]. Based on the clinical courses of our two patients, both presenting a marked discrepancy between initially silent respiratory symptoms and only slight abnormalities in imaging studies versus severe abnormalities in lung functional tests, we believe that BO is the most accurate diagnosis for these patients. Furthermore, the slight thickening of the bronchial walls observed

A

	7 yr before	3 yr before	Start	1 wk after	16 mo after
VC (L)	1.86	1.79	1.97	2.11	2.13
%VC	79	79	89	96	98
FEV1 (L)	0.94	0.60	0.65	0.93	0.99
FEV1%	50	34	33	44	46
PEFR (L/s)	2.45	1.48	1.47	2.47	2.65
V50 (L/s)	0.51	0.19	0.25	0.40	0.40
V25 (L/s)	0.21	0.08	0.07	0.12	0.14
TLC (L)	3.84	3.73	3.69	3.76	3.54
IRV (L)	0.84	0.66	0.70	0.63	0.63
TV (L)	0.58	0.46	0.46	0.68	0.63
ERV (L)	0.44	0.67	0.81	0.80	0.87
RV (L)	1.98	1.94	1.72	1.65	1.41
RV/TLC(%)	51.6	52.0	45.6	43.9	39.8
DLco	13.7		14.1	13.2	12.9
%DLco	84		92	87	85
DLco/VA	5.00		5.24	4.60	4.47



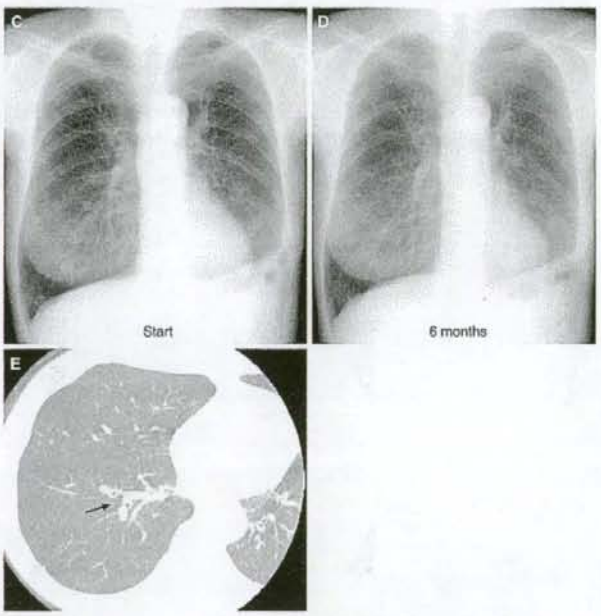


Fig. 2 a Results of pulmonary function tests in Case 2. b Flow volume curves just before ("start") and 1 week after initiation of the anticholinergic inhalation. c Chest X-ray taken before the inhalation was started. d Chest X-ray taken 6 months after anticholinergic inhalation was started. e Chest CT in the inspiratory state. *Arrow* indicates mildly thickened bronchial walls

in CT images in addition to the rapid response to anticholinergics may suggest involvement of the large airways; this may partly account for the airflow limitation in our patients. In both of our patients the obstructive ventilatory defect responded partially to an inhaled β_2-agonist. At present, however, we do not know whether an asthmatic component was involved, but their clinical courses, lacking recurrent wheeze and nocturnal dyspnea, seem obviously different from that of typical asthma. Neither blood eosinophilia, elevation of serum IgE nor a family history of

asthma was observed. Anti-asthmatic medications were tried but did not relieve dyspnea in either patient.

It is generally thought that BO is not a single disease with a uniform etiology. In addition, pathological study is often impossible in severe cases suggestive of BO. In this regard, BO "syndrome" is often used as the clinical diagnosis of this disorder in the absence of precise pathological information [7]. Collagen vascular diseases such as rheumatoid arthritis and SLE rarely accompany BO syndrome. The clinical presentation was different and specific features were not detected in our two patients. Moreover, in both patients the disease activity of SLE was low, based on the clinical and serological parameters and the SLE disease activity index (SLEDAI). In addition, recent progress in leukemia therapy has revealed that BO more often occurs following bone marrow transplantation, and that development of BO is an important factor that may limit the posttransplantation life expectancy [8, 9]. Indeed, irrespective of the nature of the primary disease, BO often progresses slowly and is highly resistant to systemic immunosuppressive therapy and β_2-agonist bronchodilators, although anecdotal reports mention a few cases that responded to immunosuppressants [6, 10]. Although the usual therapeutic regimen for BO does not include anticholinergics [11], one very recent case report suggested that an anticholinergic, inhaled tiotropium bromide, might be effective in some posttransplantation patients clinically presumed to have BO [12]. Our cases further demonstrate that anticholinergic inhalation may also be effective on autoimmune-based BO accompanying SLE and possibly other collagen diseases. At present we do not have a reasonable explanation for why anticholinergics were so effective in our patients. However, in view of that effectiveness, functional dysregulation of the cholinergic nerve system in the airways may be implicated in the pathogenesis of the airway abnormalities in our patients with SLE. We speculate that autoimmune-related airway damage may be responsible for the excessive activity of the cholinergic nerve system and the mild bronchial wall thickening seen in our patients; further assessment analyzing whether specific antibodies or subsets of lymphocytes are involved in their lung abnormalities is warranted, and, importantly, respiratory function tests revealed a decrease in the residual volume/total lung capacity (RV/TLC) ratio in both patients several months after starting medication. These results suggest that anticholinergic agents may have both early and late effects, and the late and sustained improvement of air-trapping indicates that the anticholinergics may even have affected small airway remodeling and/or the fibrosing process.

Anticholinergic agents are considered highly safe, based on the cumulative experience from extensive use of these drugs in patients with smoking-related chronic obstructive pulmonary diseases [13]. Thus, assessment of the clinical efficacy of inhaled anticholinergics seems warranted in patients with SLE or other autoimmune diseases accompanied by progressive dyspnea and obstructive respiratory abnormalities suggestive of BO.

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INTERNAL MEDICINE

ORIGINAL ARTICLE

Clinical and Radiological Features of *Pneumocystis* Pneumonia in Patients with Rheumatoid Arthritis, in comparison with Methotrexate Pneumonitis and *Pneumocystis* Pneumonia in Acquired Immunodeficiency Syndrome: A Multicenter Study

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Abstract

Objective To elucidate the clinical and radiological features of *Pneumocystis* pneumonia (PCP) in patients with rheumatoid arthritis (RA), compared with methotrexate (MTX) pneumonitis in RA and *Pneumocystis* pneumonia in acquired immunodeficiency syndrome (AIDS).

Subjects and Methods Retrospective analysis of 14 PCP cases in RA (RA-PCP), 10 MTX pneumonitis cases in RA (MTX-P) and 11 PCP cases in AIDS (AIDS-PCP) from 9 centers in the Kanto area in the last 6 years.

Results Compared with AIDS-PCP, both RA-PCP and MTX-P developed more rapidly, showing higher serum CRP and lower plasma β-D-glucan levels, and more severe oxygenation impairment. In most of the RA-PCP cases, a high dose of corticosteroid was administered as adjunctive therapy, resulting in a favorable outcome. The mortality was 14% in RA-PCP, 0% in AIDS-PCP and 0% in MTX-P cases. In RA-PCP patients the CD4 cell count showed only mild suppression, not reaching the predisposing level for PCP in HIV infection, suggesting that there are risk factors for RA-PCP other than immunosuppression. Radiologic analysis revealed some characteristic patterns of each disease. In MTX-P, diffuse homogeneous ground glass opacity (GGO) with sharp demarcation by interlobular septa (type A GGO) was found in 70%, while in AIDS-PCP diffuse, homogeneous or nonhomogeneous GGO without interlobular septal boundaries (type B GGO) was predominant (91%). In RA-PCP, type A GGO was found in 6 cases and type B GGO in 5 cases, showing the complex nature of this disease.

Conclusion RA-PCP differed considerably from AIDS-PCP clinically and radiologically. Clinically it occurred without severe immunosuppression, and showed characteristic aspects, with more intense inflammation and less parasite burden. Radiologically it mimicked MTX-P in some cases sharing the conspicuous CT features of MTX-P, rendering the distinction of these two disorders difficult.

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Key words: rheumatoid arthritis, *Pneumocystis* pneumonia, methotrexate pneumonitis, β-D-glucan, CT, acquired immunodeficiency syndrome (AIDS)

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Introduction

Pneumocystis pneumonia (PCP) is one of the uncommon but serious, life-threatening complications in patients with rheumatoid arthritis (RA) receiving treatment with methotrexate (MTX) (1-3). However it is often difficult to establish a definitive diagnosis, because the clinical and radiological presentations closely resemble those of MTX induced pneumonitis (MTX-P). Both are characterized by acute, progressive respiratory symptoms and diffuse bilateral infiltrates on chest radiography. The clue enabling a distinction lies in the detection of *Pneumocystis jirovecii* (*P. jirovecii*). However it is well known that traditional staining is often not sensitive enough in PCP in non-HIV conditions (4). Recently polymerase chain reaction (PCR) has been widely used for detection of this organism, with satisfactory sensitivity (5-7), but this method alone has the problem of false-positivity (8, 9). The subsidiary role of serology, especially measurement of β-D-glucan, has not received much attention.

We conducted a retrospective multicenter study to elucidate the clinical and radiological characteristics of RA-PCP, comparing it with MTX-P and also with AIDS-PCP , in order to discuss the problem of the differential diagnosis of these diseases.

Materials and Methods

Fourteen cases of PCP during treatment for RA were identified at 7 participating centers in Tokyo and its suburbs by practicing rheumatologists or pneumologists from April 2001 to August 2006. Ten cases of MTX-P were also identified at these centers during the same period. For comparison with RA-PCP, 11 cases of AIDS-PCP were randomly selected at two AIDS centers in Tokyo from March 2001 to December 2005. All of these cases were enrolled in the study after confirming that they had sufficient clinical information and imaging materials obtained before the beginning of definitive treatment for pulmonary events. Among them, 32 cases had thin section CT images of less than 2 mm collimation, while the other 3 cases had CT images using 5 mm collimation, both of good quality.

A diagnosis of PCP (both in RA and AIDS) was based on satisfaction of all of the following criteria; a) symptoms such as fever, cough and progressive dyspnea, associated with diffuse bilateral infiltrates on chest radiography, b) detection of *P. jirovecii* by traditional staining (Grocott or Diff-Quik or Giemsa staining) or by PCR in respiratory specimens, c) significantly elevated plasma (1→3)-β-D-glucan (β-D-glucan) level.

β-D-glucan was measured either with the β-glucan test WAKO (Wako Pure Chemical Industries, Tokyo, Japan) or with the FUNGITEC G test MK (Seikagaku Corp., Tokyo, Japan).

MTX-P was diagnosed based upon the same clinical presentations mentioned above and exclusion of infection, especially PCP, through intensive diagnostic procedures such as bronchoscopy or examination of sputum and measurement of plasma β-D-glucan. Clinical improvement following corticosteroid therapy was also taken into account.

The clinical background and preceding disease course of each patient was assessed with special attention to the dose and duration of antirheumatic drugs and also to the underlying disease. Clinical data at the recognition of the event, the clinical course and its outcome were evaluated.

Chest radiography and computed tomography (CT) were reviewed by two diagnostic radiologists. CT findings were categorized into three patterns: a) diffuse ground glass opacity (GGO) distributed in a panlobular manner, that is, GGO was sharply demarcated from the adjacent normal lung by interlobular septa (type A GGO) (Fig. 1A, Fig. 1B), b) diffuse GGO homogeneous or somewhat not homogeneous in distribution but without sharp demarcation by interlobular septa (type B GGO) (Fig. 2A, Fig. 2B), c) another pattern such as mixed consolidation and GGO (type C) (Fig. 3). The occurrence of each pattern was assessed in each group. The clinical features of each group and also their relationship with CT patterns were analyzed statistically using the Mann-Whitney-U test or Fisher's exact test.

Results

Patient characteristics

Table 1 shows the epidemiologic features of these patients. The RA-PCP group consisted of 14 patients, 2 men and 12 women, and they had a mean age of 66.5 years. *P. jirovecii* was detected in bronchoscopic specimens in 5 cases, in sputum examination in 9, by traditional staining in 3, by PCR in 11 cases. RA had been diagnosed for 11 years (mean). All had a history of receiving corticosteroid therapy and 13 patients were receiving MTX therapy (mean duration of 36.3 months) at the evolution of the lung events. Four patients were concomitantly receiving anti-TNF agents (three cases infliximab and one case etanercept). Six patients had

Figure 1A. **Type A ground glass opacity (GGO): GGO sharply demarcated from adjacent normal lung by interlobular septa. Methotrexate pneumonitis (MTX-P) was revealed in a 57-year-old woman who had received MTX therapy for 9 years for rheumatoid arthritis (RA). CT image shows homogeneous GGO which is clearly demarcated from adjacent normal lobules by interlobular septa.**

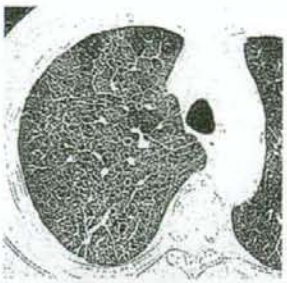

Figure 2A. **Type B GGO: homogeneous or nonhomogeneous GGO without sharp demarcation. An 83-year-old man had been treated for RA for 9 years with prednisolone (PSL) and MTX. MTX-P was diagnosed through exclusion of infection with bronchoscopy. CT shows nonhomogeneous GGO without sharp demarcation.**

Figure 1B. **Type A GGO. A case of MTX-P in a 61-year-old man. He had received MTX therapy for 7 years. He had severe respiratory distress on admission, was treated with mechanical ventilation and resulted in favorable outcome. CT shows homogeneous GGO sharply demarcated from non-affected lung by interlobular septa.**

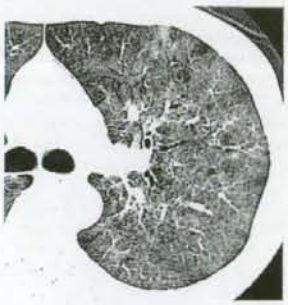

Figure 2B. **Type B GGO. A 53-year-old man had been diagnosed as HIV positive for 6 years. *Pneumocystis* pneumonia (PCP) was confirmed through positive staining for *Pneumocystis jirovecii* (*P. jirovecii*) in his sputum. CT shows diffuse, nonhomogeneous GGO without obvious demarcation.**

chronic interstitial lung disease (ILD) defined by the presence of honeycombing in CT.

The AIDS-PCP group included 11 cases, 10 men and 1 woman, with a mean age of 39.8 years. All were seropositive for the human immunodeficiency virus (HIV) antibody. *P. jirovecii* was detected by traditional staining in 5 cases and by PCR in 9.

The MTX-P group included 10 patients, 3 men and 7 women, had a mean age of 67.4 years. The diagnosis was made through exclusion of infection, especially PCP, by negative staining or PCR for *P. jirovecii* in 11 cases, and by low plasma β-D-glucan level in 2 cases. They had suffered from RA for 12 years (mean), and 7 of them had a history of corticosteroid therapy. MTX had been given for a duration of 31.0 months (mean). Two patients were concomitantly receiving anti-TNF agents (one case infliximab only once, one case etanercept). None of the patients of this group had ILD.

Clinical features

The clinical features of these three groups are shown in Table 2. Fever, cough and progressive dyspnea were predominant symptoms among all three groups. These symptoms preceded the diagnosis of the event with a period of 8.0±6.0 days in the MTX-P group, 7.6±6.4 days in the RA-PCP group, and 37.9±24.3 days in the AIDS-PCP group. The disease development was significantly faster in the MTX-P and the RA-PCP groups than the AIDS-PCP group. The serum CRP level was significantly higher in RA-PCP and MTX-P group than AIDS-PCP group (Fig. 4). The

plasma β-D-glucan level of AIDS-PCP was significantly higher (965.4 pg/ml, mean) than that of RA-PCP (98.5 pg/ml, mean). The value was below the cut-off level in MTX-P cases.

The CD4 cell count was 780.0±497.1/μl in the MTX-P group, 793.2±274.8/μl in the RA-PCP group, and 62.9±79.5/μl in the AIDS-PCP group, respectively. Taking the preserved serum immunoglobulin G (IgG) level into account, RA-PCP patients, as with MTX-P patients, showed a slight to moderate degree of immunosuppression, which was markedly different from AIDS-PCP patients (Fig. 5). PCP is usually considered to be an opportunistic infection under immunosuppressed conditions, but the immunological status was not greatly impaired in RA-PCP group. Severe hypoxemia necessitating oxygen supplementation was seen in 8 (80%) MTX-P cases, 11 (78.6%) RA-PCP cases and 3 (27.8%) AIDS-PCP cases. In summary, RA-PCP patients, along with MTX-P patients, showed more rapid clinical development, had significantly higher CRP level, lower β-D-glucan level, and worse oxygenation than AIDS-PCP patients.

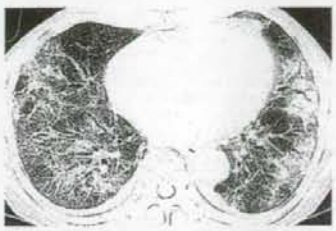

Figure 3. Type C : other type, mixed GGO and consolidation. A 69-year-old man was given a diagnosis of MTX-P. CT shows GGO intermingled with multiple foci of consolidation.

Patient outcome

All RA-PCP patients were treated with Trimethoprim-Sulfamethoxazole (TMP-SMX), together with corticosteroids (pulse therapy using methyl-prednisolone 500-1000 mg/day for 3 days in 4 cases, pulse therapy+oral prednisolone in 9 cases and oral prednisolone in 1 case). Eleven cases needed oxygen supplementation but none required mechanical ventilation. Two cases died despite intensive treatment, while the other 12 cases recovered completely within 3 or 4 weeks after admission (Table 2).

Eleven cases of the AIDS-PCP cases were treated with TMP-SMX. Adjunctive corticosteroids were given in 5 cases (oral prednisolone for 2 weeks). Three cases needed oxygen supplementation but none required mechanical ventilation. All patients recovered.

All MTX-P patients received steroid pulse therapy followed by 30-60 mg/day oral prednisolone as an initial dose with tapering. Although two cases required mechanical ven-

Table 1. **Patient Characterstics**

	MTX-P	RA-PCP	AIDS-PCP
number	10	14	11
male:female	3; 7	2;12	10; 1
age‡	67.4(46~88)	66.5(52~80)	39.8(29~58)
Detection of *P.jirovecii* organism			
bronchoscopy	(7)†	5	4
sputum		9	7
traditional staining		3(Grocott 1, Diff-Quik 2)	5(Grocott 5, Diff-Quik 3)
PCR		11	9
duration of RA(years)‡	12(3-28)	11(1-26)	
Corticosteroids user	7	14	none
Methotrexate user	10	13	none
Mtotrexate duration(mo)‡	31.0(4~104)	36.3 (1 to 78)	
anti-TNF agents	1 infliximab, 1 ethanercept	3 infliximab, 1 ethanercept	none
lung comorbidity	0	6 chronic ILD	0

† done and resulted in negative study

‡ data are shown at median (with range)

abbreviations: MTX-P = methotrexate pneumonitis, RA-PCP = *Pneumocystis* pneumonia in rheumatoid arthritis, AIDS-PCP = *Pneumocystis* pneumonia in AIDS, AIDS = acquired immunodeficiency syndrome, *P.jirovecii* = *Pneumocystis jirovecii*, Grocott = Grocott methenamine silver staining, Diff-Quik = Diff-Quik staining, PCR = polymerase chain reaction

Table 2. **Clinical Features**

	MTX-P(n=10)	RA-PCP(n=14)	AIDS-PCP(n=11)
duration of symptoms(days) before diagnosis	8.0±6.0	7.6±6.4	37.8±24.3
cough	5(50%)	5(42%)	7(64%)
fever	4(40%)	9(75%)	8(73%)
dyspnea	8(80%)	10(83%)	6(55%)
Alb (g/dl)	2.95±0.43	3.20±0.43	3.36±0.46
LDH (IU/l)	427.1±158.5	435.1±141.6	430.4±150.0
CRP (mg/dl)	11.6±6.2	8.6±4.8	2.3±2.2
KL-6 (U/ml)	814.3±757.5	1204.0±827.0	2490.8±1853.3
β-D-glucan (pg/ml)	below cut off level	98.5±94.8	969.5±1064.6
Leukocyte count(/μl)	7913.3±1851.8	8126.4±3284.3	7154.5±3433.4
Lymphocyte count (/μl)	1096.3±792.9	1028.7±599.6	963.2±684.9
CD4 cell count (/μl)	780.0±497.1	793.2±274.8	62.9±79.5
IgG (mg/dl)	1551±367	1056±340	n.d.
O_2 supplementation needed	8(80%)	11(78.6%)	3(27.8%)
ventilater needed	2(20%)	0	0
use of adjunctive corticosteroids	10(100%)	10(71.4%)	5(27.2%)
outcome(number of death)	0	2(14.3%)	0

* data are presented at median(with standard deviation)

abbreviations : Alb = serum albumin, LDH = lactate dehydrogenase, CRP = C-reactive protein, 8-D-glucan = (1→3)-8-D-glucan, IgG = immunoglobin G

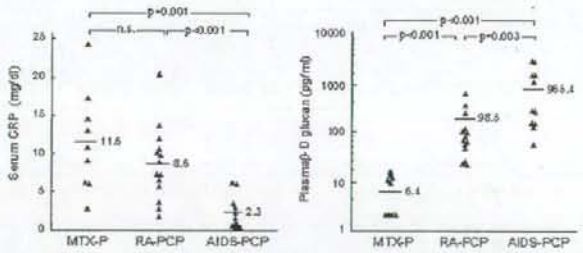

Figure 4. **Serum CRP and plasma β-D-glucan in the three groups. CRP is significantly higher in MTX-P and *Pneumocystis* pneumonia in RA patients (RA-PCP) than *Pneumocystis* pneumonia in AIDS patients (AIDS-PCP), while β-D-glucan is significantly lower in RA-PCP than AIDS-PCP.**

tilation, all recovered well.

Radiologic features

All patients showed diffuse bilateral infiltrates on chest radiography which, by itself, is neither specific nor pathognomonic for any of these three disorders. Through the analysis of CT images, we found three patterns of opacities, as mentioned above. The occurrence rates of these three patterns in each group are shown in Table 3. In the MTX-P group, the type A pattern predominated, noted in 7 cases (Fig. 1A, Fig. 1B), while type B was found in 2 (Fig. 2A), and type C in 1 case (Fig. 3). Type A was the most predominant image pattern for MTX-P. On the other hand, in the AIDS-PCP group, type A was found only in 1 case,

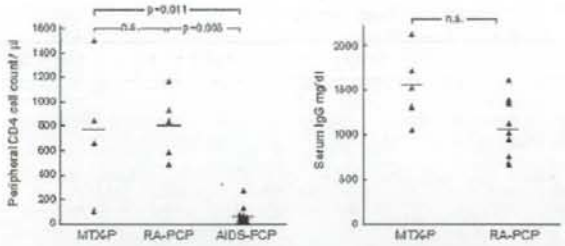

Figure 5. Immunological status of each group represented by peripheral CD4 cell count (measured in every group) and serum IgG (not measured in AIDS-PCP group). Both RA-PCP and MTX-P show a relatively preserved immunological condition in contrast with AIDS-PCP.

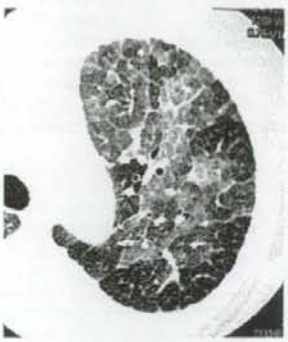

Figure 6A. GGO seen in a RA-PCP patient. A 71-year-old woman had received MTX therapy for 6 years. PCP was diagnosed based on elevated β-D-glucan and positive PCR for *P. jirovecii* in bronchoalveolar lavage fluid. CT shows type A GGO.

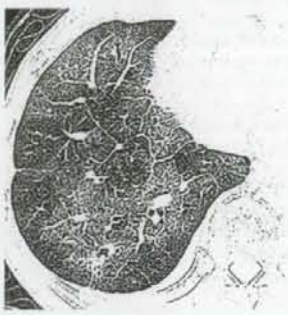

Figure 6B. GGO seen in a RA-PCP patient. A 64-year-old man had received MTX therapy for 5 years. *P. jirovecii* was identified with Grocott staining with marked elevation of serum β-D-glucan. CT shows type B GGO, nonhomogeneous pattern without lobule to lobule demarcation.

while the other 10 cases showed type B (Fig. 2B), suggesting type B to be the typical image pattern of this disease. Among the RA-PCP group, 6 cases showed type A pattern (Fig. 6A), 5 cases showed type B (Fig. 6B), and three cases type C, showing the complex nature of this disorder. The occurrence of type A GGO in RA-PCP did not differ significantly from that of MTX-P. We analyzed the relationship of these image patterns in CT and clinical features, but failed to find any relevance (data not shown).

Discussion

MTX is now widely used for the treatment of RA, because of its efficacy and low toxicity. In association with the increased use of MTX, serious and life-threatening lung complications have been increasingly reported (1-4, 10-12). One is PCP and another is MTX-P. Both diseases develop acutely and may sometimes result in serious consequences. PCP is an infectious disease in an immunosuppressed condition and should be treated with antimicrobial agents. MTX-P is a hypersensitivity reaction and should be treated by withdrawal of MTX, often followed by corticosteroids. To distinguish between these two conditions, RA-PCP and MTX-P, is therefore very important in the clinical context of acute onset lung injury during the treatment for RA with MTX.

The distinction, however, is often very difficult to make because of their similar clinical presentations. Imaging features are also so similar that no definitive difference has been reported between the two. Above all, the detection of *P. jirovecii*, which is mandatory for the diagnosis of PCP, is often very difficult in RA-PCP patients. In PCP patients without AIDS such as those of connective tissue disorders (CTD) receiving immunomosuppresive therapy (13), it is well documented that the organism numbers of *P. jirovecii* are significantly fewer in respiratory specimens (14-17). In

Table 3. **Occurrence of CT Image Patterns**

	MTX-P (n=10)	RA-PCP (n=14)	AIDS-PCP (n=11)
type A	7	6	1
type B	2	5	10
type C	1	3	0

type A, type B, type C : see text

such a situation, traditional staining is often not sufficiently sensitive. PCR for *P. jirovecii* is a much more sensitive technique than traditional staining (5) and its usefulness in the diagnosis of PCP, especially with low organism burden, was reported by many investigators (4, 6, 7). On the other hand several studies found incontrovertible incidence of colonization of *P. jirovecii* among immunosuppressed patients, suggesting that a positive PCR result alone may lead to overdiagnosis (8, 9). Meanwhile the measurement of β-D-glucan, a quantitative marker for mycotic diseases, has been reported as a useful and reliable marker in the diagnosis of PCP (18-21). Thus, we considered that, for the diagnosis of RA-PCP, detection of *P. jirovecii* by traditional staining is desirable but cases of positive PCR results with negative smears are also eligible when the plasma β-D-glucan level is significantly elevated.

Radiologic features of MTX-P

The radiologic features of MTX-P have been reported by many authors (10-12). They have been noted only as diffuse infiltrates on radiography and GGO on CT, with no further details described. Through the analysis of CT images of our cases, we found conspicuous features of MTX-P, that is, type A GGO as the predominant pattern on CT, which has never been reported.

RA-PCP compared to AIDS-PCP

Several important differences were found between the two groups clinically and radiologically. RA-PCP developed more rapidly than AIDS-PCP. Respiratory impairment was more severe in RA-PCP, and resulted in two deaths, while there was no fatality in the AIDS-PCP group. The level of plasma β-D-glucan, a quantitative marker for *P. jirovecii*, was significantly lower compared to AIDS-PCP, suggesting a lower organism burden in RA-PCP cases. All these differences have been well documented in many studies as the differences of PCP in patients with and without AIDS (13-17). Limper et al conducted a clinicopathological and comparative study of PCP of both conditions, including quantitative assay of *P. jirovecii* and inflammatory cells in BAL fluid, demonstrating fewer parasite numbers and more intense lung inflammation and also severe clinical symptoms in non-HIV PCP (15).

It is noteworthy that in our RA-PCP patients, the immunological status was not impaired as severely as in AIDS-PCP patients. These facts, i.e., relatively preserved immunity in RA-PCP patients, have been pointed out in several reports (22, 23). Why PCP can occur in patients who are not severely immunosuppressed is a problem to be solved, especially in relation to some particular immunomodifying actions of anti-rheumatic drugs.

The radiologic features of AIDS-PCP have been extensively reported (24-26), but not as thoroughly for non-AIDS-PCP or for the difference between the two, PCP with and without AIDS. Through detailed radiologic analysis, we found differences between these two disorders, which have apparently never been documented previously. In most AIDS-PCP cases, CT presented type B GGO. We consider this finding, which coincides with features previously reported (26-28), to be characteristic of this disease. However, in 6 of the 14 RA-PCP cases, CT showed type A GGO, while 5 presented type B GGO. RA-PCP showed complex radiological findings, intermediate between AIDS-PCP and MTX-P. Since the radiologic features might reflect the pathophysiology of each disease, we conducted a comparative analysis of the CT patterns and the clinical features of each disease, but failed to demonstrate any correlation, either with the clinical features or with patient outcome.

In all 14 cases of RA-PCP, corticosteroid was administered concomitantly with TMP-SMX. Two died, the mortality rate being 14%. High mortality has been reported in PCP of CTD (33% Sekowitz, 32% Godeau et al) (13, 22), to be much higher than AIDS-PCP. It is suggested that the good outcome of the present cases was the result of the use of corticosteroids added to TMP-SMX.

In AIDS-PCP, the National Institutes of Health - University of California Expert Panel recommends use of steroids as early as possible (27). In those cases, the inflammatory response evoked by *P. jirovecii* is assumed to contribute to the lung damage, indicating the need for corticosteroid treatment. However for RA-PCP or PCP of CTD in general, the validity of corticosteroid use has not been discussed in depth. Pareja et al retrospectively analyzed the clinical course of 30 cases of severe PCP without AIDS, among

whom 16 cases were treated with adjunctive corticosteroids (28). They reported good clinical outcome in patients who received high doses of adjunctive corticosteroids. In RA-PCP, the host inflammatory response is assumed to be more intense, in spite of lower organism burden, contributing to severe lung injury. It is therefore reasonable that corticosteroids may play a beneficial role in treatment of RA-PCP, when used concomitantly with antipneumocystic drugs. This issue should be examined in a prospective study.

Discrimination between RA-PCP and MTX-P

Comparison of clinical features of RA-PCP and MTX-P revealed their close resemblance, in terms of major symptoms, rapid progression, and severe oxygenation impairment. Levels of serum albumin, LDH, CRP, and KL-6 were also similar. Immunological status at presentation was also preserved relatively well in both groups. Thus, in the clinical setting of an acute respiratory event in a patient under MTX treatment for RA, discrimination between RA-PCP and MTX-P is challenging.

CT features have limited usefulness. When CT shows GGO of type A pattern or Type B pattern, MTX-P as well as RA-PCP are equally likely, because these patterns are seen in both diseases. Distinction is impossible by CT imaging alone. Thus the discrimination of RA-PCP from MTX-P should be based on detection of *P. jirovecii*, combined with serology.

In RA patients under MTX treatment with acute onset lung injury, we should treat them as MTX-P with corticosteroids, if *P. jirovecii* is not detected. If traditional staining or PCR reveals *P. jirovecii*, along with elevated plasma β-D-glucan level, we should treat it as RA-PCP, with antipneumocystic drugs. Use of adjunctive steroids is a matter to be examined in future.

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ORIGINAL ARTICLE

Psychological Stress Evaluation of Patients with Bronchial Asthma Based on the Chromogranin A Level in Saliva

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To evaluate the involvement of stress in asthmatics we measured the concentration of chromogranin A (CgA) in saliva as an indicator of psychological stress and investigated its correlation with peak expiratory flow (PEF), a visual analog scale (VAS) score of symptoms, and the score of the Short-form 36 health survey questionnaire (SF-36) in 62 adult asthmatics. CgA had a significant correlation with role physical (RP) ($r = -0.298$, $p < 0.05$), role emotional (RE) ($r = -0.294$, $p < 0.05$) and the physical component summary (PCS) ($r = -0.310$, $p < 0.05$) of SF-36, and VAS score ($r = -0.435$, $p < 0.01$). We concluded that the concentration of CgA reflects the stress in asthmatics caused by work or daily life limitations.

Keywords bronchial asthma, salivary chromogranin A, Short-form 36 health survey questionnaire (SF-36),% peak expiratory flow, visual analog scale (VAS)

INTRODUCTION

It has been reported that patients with asthma may experience psychological and social problems (1–3). The purpose of this study is to evaluate the stress experienced by asthmatics by measuring the concentration of CgA in saliva as an indicator of psychological stress (4) and comparing it with the stress scored by the score of the Short-form 36 health survey questionnaire (SF-36) as an indicator of QOL (5), percent peak expiratory flow (%PEF) as an indicator of clinical airway obstruction, and a visual analog scale (VAS) score as an indicator of symptoms of patients with asthma.

METHODS

The total number of subjects with asthma was 62 (34 males, 28 females), and the average age was 57.6 ± 13.4 years old (mean ± SD). We enrolled randomly as subjects for this study asthmatics who were regularly visiting the asthma outpatient clinic of the Third Department of Internal Medicine of Iwate Medical University.

We explained the purpose and method of the study, and both verbal and written consent were obtained from all participants in this study.

All the subjects were classified as having asthma according to the GINA 2006 standard (2006 Global Initiative for Asthma) (6). The degree of control by therapy was divided into three groups (controlled, partly controlled, and uncontrolled), based on the following criteria: daytime symptoms, limitations of activities, nocturnal symptoms/awakening, the need for reliever/rescue treatment, lung functions (PEF or FEV_1), and exacerbations. The present subjects consisted of 36 who were controlled, 26 who were partly controlled, and 0 who were uncontrolled. Moreover, the therapeutic control level based on the severity was classified from step 1 to step 5, with 9 subjects at step 1, 26 at step 2, 2 at step 3, 18 at step 4, and 7 at step 5 (Table 1).

The breakdown of drugs used in this study was 80.6% steroid inhalant, 38.7% long-acting $\beta 2$ stimulator (inhalant and patch), and 11.3% oral steroid (regular use) (Table 1).

We measured the concentration of CgA in the saliva at the beginning of the test subjects' visits to the asthma clinic. After the subjects had 5 minutes of rest while seated, we sampled the saliva using Salivette® (Salstedt, Germany).

A cylindrical piece of cotton was placed beside the tongue in the oral cavity, so that secreted saliva was absorbed by the cotton for 3 minutes. Thereafter, we placed a sample into a small tube for frozen storage at −80°C.

The concentration of CgA in the saliva was determined by the EIA method using a YKO 70 Human Chromogranin A EIA (enzyme immunoassay) kit (Yanaihara Institute Inc., Shizuoka, Japan) (7).

We asked the subjects to complete the SF-36, which is a questionnaire for quality of life (QOL) evaluation. The SF-36 is a self-administered questionnaire consisting of 36 items, and the QOL for the past month was evaluated for 8 items, including (1) physical functioning (PF), (2) bodily pain (BP), (3) vitality (VT), (4) mental health (MH), (5) role physical (RP), (6) general health perception (GH), (7) social functioning (SF), and (8) role emotional (RE). The score of each item consisted of 0 to 100 points, and the higher the score, the better the QOL. Furthermore, these 8 items were separated into two factors, physical health and mental health, based on the factor structure and were also corrected so that the standard value became 50 ± 10 points as the physical component summary (PCS) or the mental component summary (MCS), and each score was calculated (4).

Next, using a peak flow meter (Mini-Wright Peak Flow Meter®, Clement Clarke Int., UK), the peak expiratory flow on the day of the examination was measured and the percent peak expiratory flow (peak expiratory flow measured/peak expiratory flow predicted, %PEF) was calculated as an indicator of airflow obstruction.

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