Table 3 Clinical and CT characteristics of drug-induced pneumonitis caused by Sai-rei-to

Reporter	Age Sex	Duration of medication (days)	WBC (/μl)	CRP (mg/dl)	LDH (IU/l)	KL-6 (U/ml)	CT findings	DLST	BALF TCC (×10⁵/ml)	BALF Lym (%)	BALF CD4/8
Yamawaki[6]	66/F	22	10,030	12.1	750	NR	Fine reticular opacities	+	2.83	47	0.33
Yamawaki[7]	74/M	110	9,840	23.2	703	NR	Consolidtion, GGO Pleural effusion	−	ND		
Maeno[8]	51/F	90	5,300	< 0.3	481	NR	GGO Atelectasis	−*	1.0	70.9	0.14
Shinohara[9]	61/M	45	9,180	3	592	NR	GGO	+	5.0	53	0.07
Arimoto[10]	54/M	about 30	7,400	5.05	814	NR	GGO	+	3.0	60	0.12
Sakamoto[11]	68/M	8	9,600	11.1	936	ND	GGO Consolidation	−		ND	
Sakamoto[11]	52/M	49	11,400	17.7	1,037	1,120	GGO	ND		ND	
Itoh[12]	77/M	5	13,130	3.71	722	364	GGO Consolidation	+	2.2	21	1.0
Takayama[13]	65/F	about 100	8,000	6.7	431	515	GGO	+	31	14	0.20
Tanoue[14]	52/F	23	9,600	23.2	1,235	ND	GGO Reticulation	−	2.0	52	0.20
Our case	38/M	40	12,600	1.67	480	849	GGO Consolidation Reticulation	+	2.5	33	0.16

* a test of bronchoalveolar lavage fluid was positive. NR: not recorded, ND: not done, GGO: ground glass opacity, DLST: drug lymphocyte stimulating test

間は5日から110日であった．検査所見ではWBCの上昇の他，診断基準に入っていないが，CRP，LDHの上昇を認める例が多かった．漢方による薬剤性肺炎の組織像として器質化肺炎，胞隔炎，好酸球性肺炎等の報告があり，画像上多くはスリガラス影・浸潤影を呈し，小葉間隔壁の肥厚・網状影を伴うこともある．またBALF中リンパ球比率の増加，CD4/8比は低下を認めるという．これらにはアレルギー性機序が関与していると推察されるが，同じ漢方薬である小柴胡湯では細胞傷害の機序が働いたとの報告もあり[15]，一概に論ずることは難しいと思われる．DLST陽性を示したものは11例中本例を含め6例であった．DLSTは薬剤に感作されたリンパ球が，抗原である薬剤と反応して分裂・増殖する反応を応用した検査である．しかし薬剤自体がリンパ球を直接刺激する作用を有していると薬剤の抗原性に基づく結果を反映することにはならず，また薬剤濃度が考慮されずに希釈系列上の最高値を見ているといった問題点がある．また薬剤の種類にもかかわらず，判定基準が一定であることにも問題がある．DLSTは一律にStimulation Indexが180%未満が陰性，180～200%が偽陽性，200%以上を陽性としているが田村らの診断基準にもあるように，陽性であれば薬剤性肺炎の有用な根拠となり，DLSTが重要視されているが，その解釈についてはいつも注意を払わないといけない．本例はStimulation Indexが181%であったが，臨床経過から柴苓湯の関与が明白と思われ，陽性として扱った．柴苓湯は小柴胡湯と五苓散の合剤であり，小柴胡湯に含まれる黄芩による薬剤性肺炎の報告が散見[16]されることから黄芩の関与が考えられるが，本例においては生薬ごとのDLSTは施行しておらず不明である．漢方薬は複数の生薬から構成されておりその相互作用という観点からも検討を要すると思われた．

結　語

柴苓湯のDLST陽性で他の被疑薬2剤の再投与試験陰性より診断し得た，柴苓湯による薬剤性肺炎の1例を報告した．

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Abstract

A case of drug-induced pneumonitis due to Sai-rei-to

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The patient was given Sai-rei-to, adenosine triphosphate disodium and Mecobalamin on a diagnosis of sudden deafness. Forty days later, exertional dyspnea and cough appeared. He was given a diagnosis of bacterial pneumonia and was treated with several antibiotics. His respiratory state gradually worsened and he was refered to our hospital. His chest computed tomography scan showed ground-glass opacity, with consolidation, and laboratory data showed high values of white blood cell and liver dysfunction. After halting all medicines, he recovered. Because the lymphocyte stimulation test was positive for Sai-rei-to and he was still well after taking adenosine triphosphate disodium and Mecobalamin, we diagnosed drug-induced pneumonitis caused by Sai-rei-to.

●症 例

著明な細気管支病変を呈した夏型過敏性肺炎の2例

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要旨：症例は56歳男性および53歳女性．共に夏に咳嗽，喀痰，呼吸困難で発症，胸部CTにてスリガラス影に加え，びまん性汎細気管支炎様の細気管支病変を認めた．両者とも低酸素血症を呈し，抗トリコスポロン抗体と帰宅試験が陽性であり，さらに胸腔鏡下肺生検にて細気管支領域に肉芽腫性病変を認めたことから夏型過敏性肺炎と診断し，抗原隔離とステロイド投与を行った．画像，呼吸機能および病理像で細気管支病変が目立つ夏型過敏性肺炎が存在することを念頭に入れておく必要がある．

キーワード：夏型過敏性肺炎，細気管支病変，閉塞性換気障害，胸腔鏡下肺生検
Summer-type hypersensitivity pneumonitis, Bronchiole lesion,
Obstructive ventilatory defect, Lung biopsy under video-assisted thoracoscopy

緒 言

過敏性肺炎（hypersensitivity pneumonitis；以下HP）は有機物の抗原あるいは無機物の化学物質を反復吸入しているうちにこれに感作されて，III型及びIV型アレルギー反応が細気管支から肺胞にかけて起こる結果発症するびまん性肉芽腫性間質性肺炎の総称である．呼吸機能では一般に拘束性障害を認め，CTではスリガラス影や小葉中心性の小結節影を示すことが多い[1]．今回我々は，画像上一見びまん性汎細気管支炎を思わせる小葉中心性に分布する粒状影とそれにつながる樹枝状影を呈し，胸腔鏡下肺生検で細気管支に強い病変を認めた夏型過敏性肺炎（Summer-type HP；以下SHP）の2例を経験したので報告する．

症 例

症例1：56歳，男性．

主訴：咳嗽，喀痰，呼吸困難．

既往歴：特記事項なし．

家族歴：特記事項なし．

生活歴：職業歴：車部品組み立て，アスベスト曝露歴なし．

喫煙歴：20本×36年．

住宅：木造築20年．日当たり・風通し不良，湿気多い．

現病歴：55歳の夏に咳嗽，呼吸困難を自覚したが冬には自然に軽快した．翌年8月から再び咳嗽，喀痰，呼吸困難が出現，増悪するため同年9月当院に紹介．

入院時現症：身長171cm，体重55kg，血圧170/80 mmHg，脈拍122回/分・整．バチ状指なし．皮疹なし．表在リンパ節触知せず．心音異常なし．両肺にてfine cracklesを聴取．腹部触診上異常なし．

入院時検査成績（Table 1）：白血球11,500/μl．CRP 3.9mg/dlと上昇していた．動脈血液ガスではPaO_2が51.1Torr，$PaCO_2$が50.4TorrとII型呼吸不全を呈していた．呼吸機能検査では著明な%VCの低下，$FEV_{1.0}$%の低下を認めた．右B^4で施行した気管支肺胞洗浄では，有意な菌は検出されなかったが，好中球が72%と増加，CD4/8は0.21と低下していた．また，血清抗トリコスポロン抗体は，512倍と高値であった．

胸部画像所見（Fig. 1）：びまん性のスリガラス影と小葉中心性のごく淡い小粒状影とそれにつながる樹枝状陰影を認めた．

経過：当初，細菌性細気管支炎の可能性を考えlevofloxacin，clarithromycinを1週間投与したが改善を認めず，投与を中止した．その後緩徐に画像所見の改善がみられ，抗トリコスポロン抗体の陽性が判明しHPを疑ったが，気管支肺胞洗浄で好中球が優位であったこと，画像所見が非典型的であったことなどから，第15病日に右S^8にて胸腔鏡下肺生検を施行した（Fig. 2）．病理学的所見では小葉中心性の軽い細胞性間質性肺炎を背景に，壊死性肉芽腫性病変が細気管支をほぼ閉塞しbronchocentric granuloma様の所見を認めた．以上の結

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（受付日平成20年6月20日）

Table 1 Laboratory data on admission (Case1)

Hematology		Serology	
WBC	11,500/μl	CRP	3.9 mg/dl
Neut	70%	IgG	1,800 mg/dl
Baso	0%	IgA	425 mg/dl
Lym	27%	IgM	107 mg/dl
Mono	1%	IgE	50 IU/ml
Eos	2%	Antinuclear antibody	< ×20
RBC	512×10^4/μl	Antitrichosporon antibody	×640
Hb	15.8 g/dl	Blood Gas Analysis (room air)	
Ht	46.8%	pH	7.44
Plt	25.5×10^4/μl	PaO_2	51.1 Torr
Biochemistry		$PaCO_2$	50.4 Torr
TP	8 g/dl	Pulmonary Function Test	
T-Bil	0.5 mg/dl	VC	0.87 *l*
LDH	183 IU/*l*	%VC	23.8%
ALP	388 IU/*l*	$FEV_{1.0}$%	65.0%
AST	20 IU/*l*	BAL analysis (rt B^4)	
ALT	13 IU/*l*	Recovery	47/150 ml
BUN	19 mg/dl	Total cell counts	6.3×10^5/ml
Cr	1.0 mg/dl	Eos	1%
		Neut	72%
		Lym	15%
		Mψ	12%
		CD4/CD8	0.21

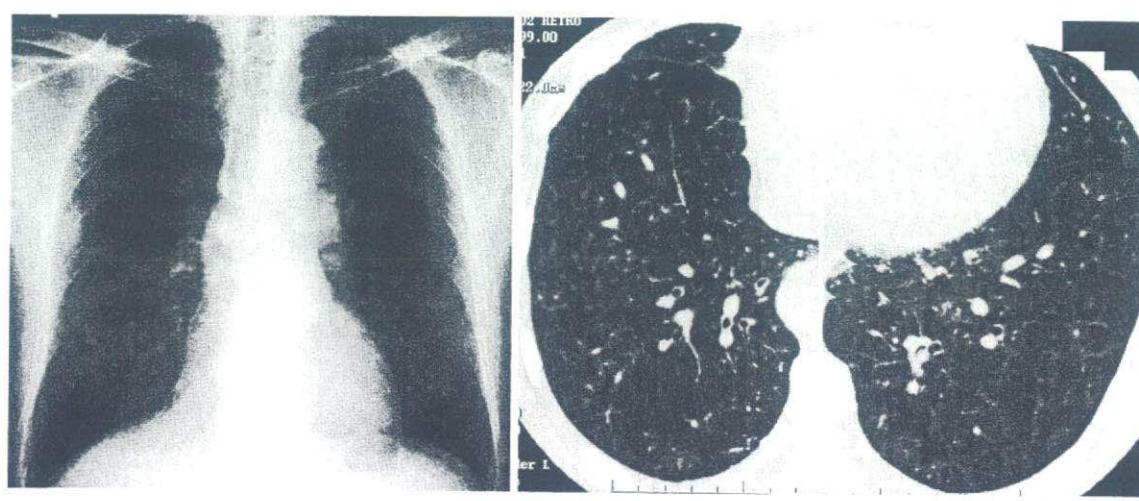

Fig. 1 Chest radiograph and CT scan on admission of Case 1 showing diffuse small nodular lesions with diffuse ground-glass opacity in both lung fields.

果と帰宅試験が陽性であったことから，SHPと診断した．抗原回避だけでは自覚症状・画像所見の改善に乏しく，第42病日から3日間methylprednisolone 1gを投与した後，prednisolone（以下PSL）30mgの投与を開始，これにより自覚症状は著明に改善し，PaO_2は50Torrから80Torrに，$FEV_{1.0}$%は59%から66%にそれぞれ上昇したため，PSLは漸減中止した．翌年5月末に再燃し再入院となったが，このときはステロイドを用いず入院による抗原回避のみで軽快した．娘宅で生活することを条件に8月に退院したが，その後も，毎日短時間ずつ自宅に戻っており，10月頃再燃，1週間のみPSLを投与し軽快した．翌年6月転居しその後再発はない．

症例2：53歳，女性．

主訴：喀痰，咳嗽，発熱．

既往歴：49歳時，気管支喘息，50歳時，肺炎．

家族歴：母：気管支喘息．

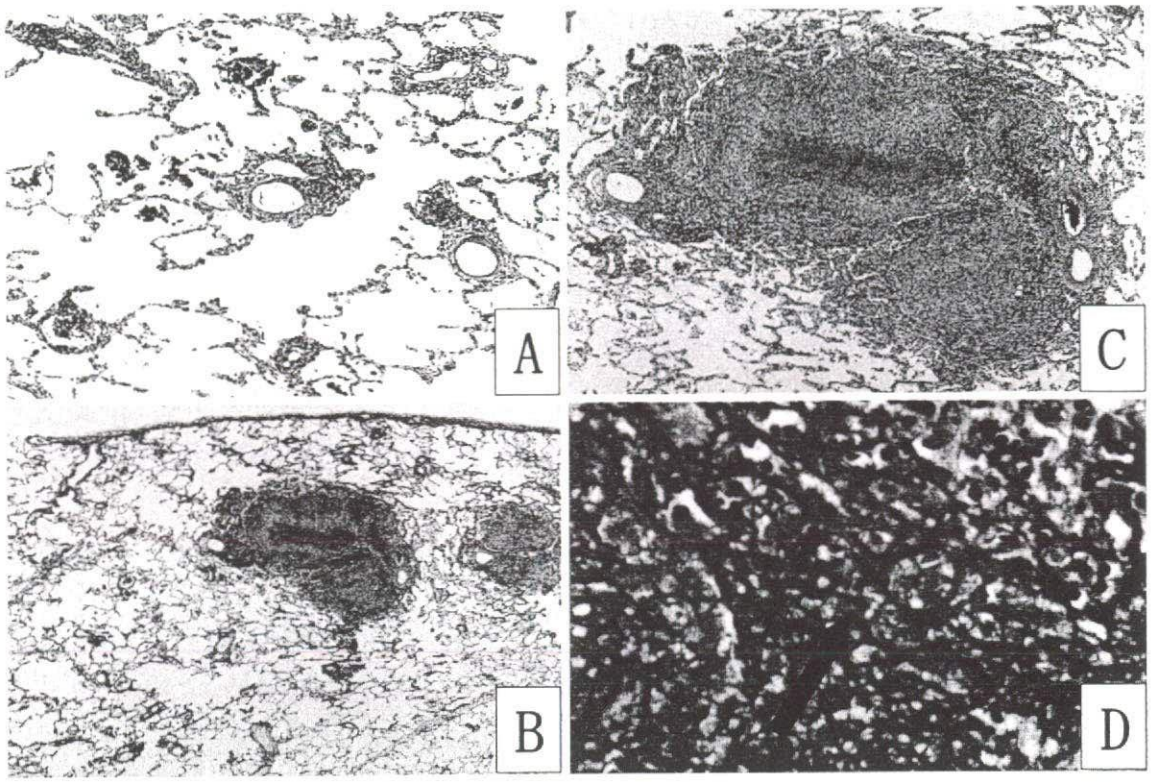

Fig. 2 VATS biopsy of Case 1. A, B, C: Granuloma with necrosis in the center. The granuloma is buried in the air duct and spreads in the periphery of the air duct. D: Trichosporon spore in a necrotic area.

Table 2 Laboratory data on admisson (Case2)

Hematology		Serology	
WBC	7,800/μl	CRP	0.20 mg/dl
Neut	48.3%	IgG	1,476 mg/dl
Baso	0.9%	IgA	461 mg/dl
Lym	32.2%	IgE	172 IU/ml
Mono	6.3%	Antinuclear antibody	×320
Eos	12.3%	Antitrichosporon antibody	×32
RBC	455×10^4/μl	Anti pigeon dropping extract antibody (−)	
Hb	13.4 g/dl	Blood Gas Analysis (room air)	
Ht	39.9%	pH	7.425
Plt	39.5×10^4/μl	PaO_2	51.0 Torr
Biochemistry		$PaCO_2$	55.0 Torr
TP	7.0 g/dl	Pulmonary Function Test	
T-Bil	0.4 mg/dl	VC	2.19 *l*
LDH	175 IU/*l*	%VC	79.3%
ALP	217 IU/*l*	$FEV_{1.0}$%	59.3%
AST	20 IU/*l*	%DLco	35.4%
ALT	10 IU/*l*	BAL analysis (rt B^4)	
BUN	6 mg/dl	Recovery	81/150 ml
Cr	0.5 mg/dl	Total cell counts	7.0×10^5/ml
		Eos	2%
		Neut	10%
		Lymp	67%
		Mψ	21%
		CD4/CD8	0.69

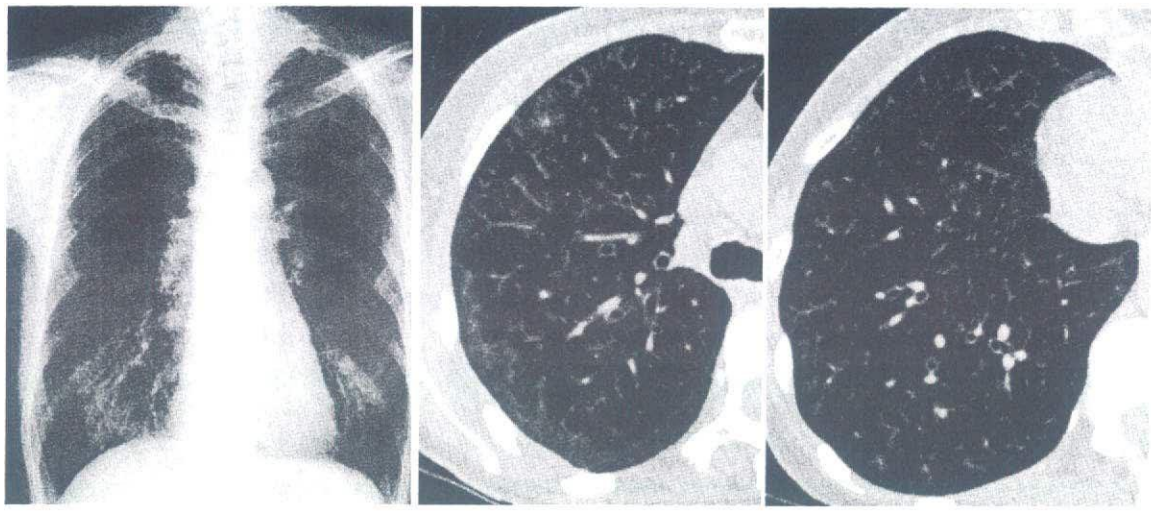

Fig. 3 Chest radiograph and CT scan on admission of Case 2 showing diffuse panbronchiolitis-like centrilobular small nodules and ground-glass appearance.

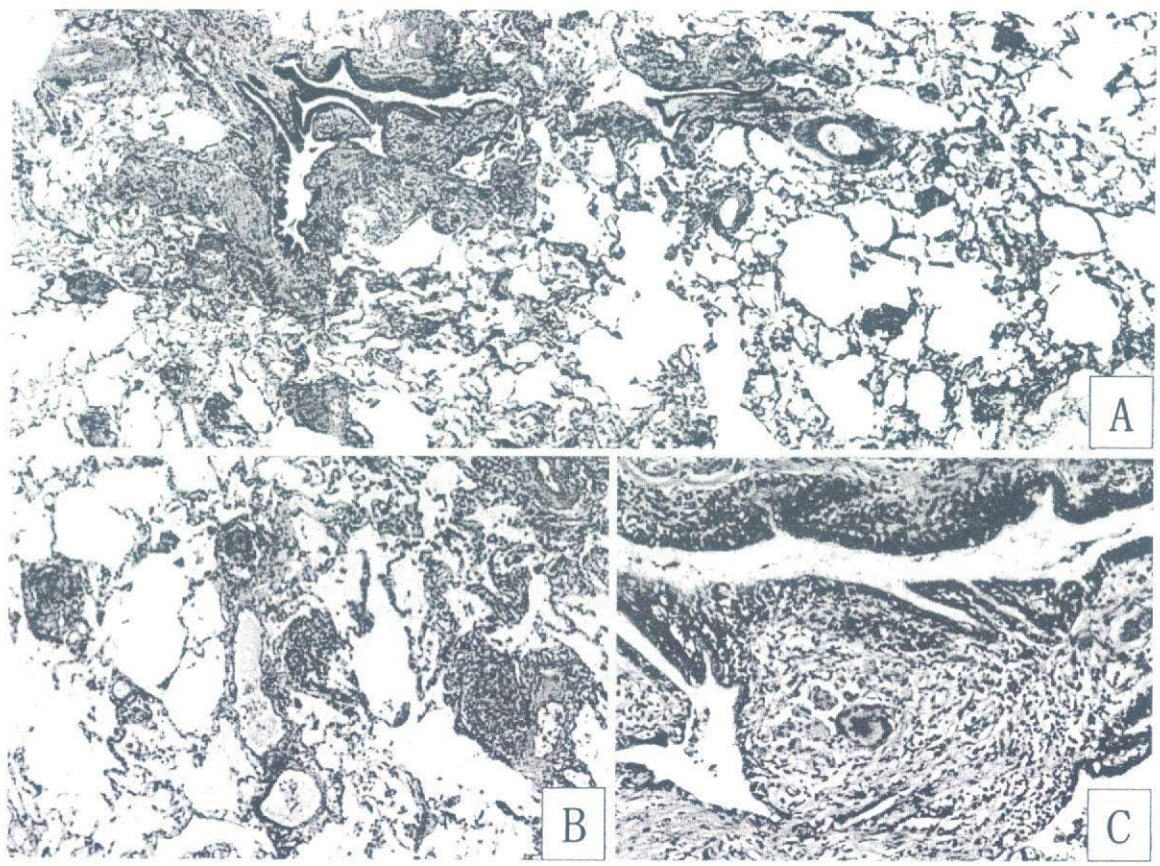

Fig. 4 VATS biopsy of Case 2. A, B: Lumen of membranaceous bronchiole is narrowed by severe invasion of inflammatory cells. C: Some granulomas without necrosis are detected in S^9.

生活歴：職業歴：23～50歳；鉄工所で研磨工として従事．喫煙歴：40本×30年．

住宅：木造築50年の住居に10年前より居住．日当たり・風通し不良，湿気多い．5～6年前よりベランダに鳩が20羽程度飛来し糞が多量に付着．

現病歴：50歳時に肺炎に罹患後，体重が3年で7kg減少していた．3年後の6月下旬から咳嗽，喀痰，37～38℃の発熱を認めるようになり近医受診，肺炎と診断され抗菌薬の投与を受けるも改善なく，7月に当院紹介となった．当初細菌性細気管支炎の関与も考え，外来にてlevofloxacin，clarithromycinを投与したところ症状増悪したため，8月に精査・加療目的にて入院となった．

入院時現症：身長167cm，体重44kg，体温36.8℃，血圧94/64mmHg，脈拍85回/分・整．皮疹なし．チアノーゼなし．バチ状指なし．表在リンパ節触知せず．心雑音なし．両下肺でcoarse crackles聴取．腹部異常なし．神経学的異常なし．

入院時検査所見（Table 2）：末梢血好酸球分画が12.3%，IgEが172IU/mlと上昇，KL-6も1,340U/mlと上昇していた．血液ガス検査では$PaCO_2$ 55Torr，PaO_2 51TorrとII型呼吸不全を認め，呼吸機能検査では$FEV_{1.0}$%が59.3%，%DL_{CO}が35.4%と低下していた．右B^4で施行した気管支肺胞洗浄ではリンパ球比率が67%と上昇，CD4/8は0.69と低下していた．血清中の抗トリコスポロン抗体は32倍と陽性であり，鳩排泄物抽出物に対する血清IgG抗体は陰性であった．

胸部画像所見（Fig. 3）：びまん性に広がるスリガラス影と小葉中心性の粒状影とそれにつながる樹枝状影を認めた．

入院後経過：入院後無治療で徐々に喀痰・咳嗽は減少，PaO_2は72Torr，%VCは84%，$FEV_{1.0}$%は70%にそれぞれ改善し画像上の改善も認めた．7月発症であること，気管支肺胞洗浄液中のリンパ球が増加していたこと，抗トリコスポロン抗体が陽性であったことよりSHPを疑ったが，HRCTではスリガラス影と共に粒状影とそれにつながる樹枝状陰影を認め，閉塞性換気障害が強く，非典型的な点が存在することから胸腔鏡下肺生検を施行した．病理組織をFig. 4に示す．

終末細気管支から呼吸細気管支にかけての細気管支に病変の主座を認め，気管支周囲には炎症細胞が浸潤し線維化が広がっており，細気管支内腔を狭小化するような病変を認めた．また一部好酸球浸潤を認め，周囲の肺胞壁には壊死を伴わない肉芽腫が散見された．本例も軽い細胞性間質性肺炎を背景に認めた．9月12日より帰宅試験を実施したところ，帰宅3日目には咳嗽・喀痰の増加と呼吸困難が出現，PaO_2は72Torrから61Torrへ，%VCは79%から61%へ，$FEV_{1.0}$%は70%から62%に低下し，帰宅試験陽性とした．娘宅で生活することを条件に9月30日に一度退院となったが，自宅に戻ることを強く希望したため11月からPSL 40mgより内服を開始した．PSL内服下で帰宅試験を再度実施したが，やはり陽性であり，自宅に戻ることは断念，転居となった．以後再然せず経過している．

考　察

厚生省特定疾患「びまん性肺疾患」調査研究班（1990年）過敏性肺臓炎診断の手引きと診断基準[2]によると（1）咳嗽，呼吸困難，発熱を認めること（2）画像上のびまん性小粒状影，拘束性換気障害，PaO_2の低下を認めること，気管支肺胞洗浄液中のリンパ球の増加を認めること，（3）7月に発症していること，（4）抗トリコスポロン抗体が陽性であること，（5）環境曝露による臨床像の再現されること，（6）病理学的に肉芽腫，胞隔炎を認めるものをHPと診断するが自験例はいずれもこの基準を満たす．しかし両者ともHPとしては非常に喀痰が多く，画像上一見びまん性汎細気管支炎を思わせる陰影を呈した点，呼吸機能では拘束性障害に加え，閉塞性障害を認めた点が非典型的であった．

胸腔鏡下肺生検では細気管支を閉塞するように肉芽腫や細胞浸潤を認め，これによりCTで細気管支病変を思わせる陰影を呈し，閉塞性障害を増悪させた可能性が高い．

HPと細気管支病変および閉塞性換気障害との関連については文献上いくつかの報告がある．Sutinenらは HPの90%以上で病理学的に細気管支レベルに炎症性変化と肉芽腫を認め，さらに約16%に気管支閉塞の所見がみられるとした[3]．

Warrenらは HP 14例中3例でflow-volume曲線のスロープ低下[4]を，Kokkarinenらは農夫肺101例中約12%の症例で$FEV_{1.0}$%の低下[5]を認めたとしている．

またKarrらの喘息様症状を伴った農夫肺症例[6]，有田らのびまん性汎細気管支炎様のHP症例[7]，岩神らの著明な閉塞性換気障害を示したSHPの1例[8]，伊佐治らのcentrilobular branching opacitiesを主所見としたSHPの1例[9]などの症例報告があり，両者の関連が議論されるようになってきている．HPにおいて細気管支病変が強く出る機序に関して自験例から，次のように検討してみた．

症例1では組織学的にトリコスポロン様の胞子と思われる構造物を認めたこと，トリコスポロン抗体価が非常に高いことから，抗原曝露量が多いことが推測され，このような大量の抗原吸入がある種の感染を成立させ，BALFの好中球増加につながった可能性や細気管支病変を引き起こした可能性を考えた．急性期のHPにてBALF好中球の増加がいわれているが[10]，本例は急性発症とはいいがたい．

また喫煙との関係に関しても注目してみた．疫学的にHPは非喫煙者に多いことから喫煙そのものはHPの免疫反応を減弱させると考えられているが[11][12]，自験例がなぜ閉塞性障害の強いHPを発症したのか推測の域は出ないが，喫煙による気流制限に伴ってHPの病変の主座をより中枢に移行させた可能性，最初から喫煙による閉塞性換気障害がありそれにSHPの拘束性換気障害が加わった可能性などが考えられる．また増加した喀痰も閉塞性換気障害を顕在化させた理由であろう．SHPに細気管支病変と閉塞性換気障害を合併する症例はまだ少な

く今後，症例の蓄積が必要であると考えられた．

以上，病理学的に強い細気管支病変を認め，肺機能検査上も閉塞性障害を来たしたSHPの2症例を報告した．

謝辞：本稿を終えるにあたり，本症例の特異抗体の検査を施行していただきました旧府立羽曳野病院アレルギー研究室浜上小夜先生，宮川トシ先生および東京医科歯科大学呼吸器内科大谷義夫先生に深謝いたします．

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Abstract

Two cases of summer-type hypersensitivity peumonitis with remarkable changes in the bronchioles

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A 56-year-old man and a 53-year-old woman with cough, sputum and dyspnea were admitted in the summer. High-resolution computed tomographic findings of the chest showed centrilobular branching opacities like diffuse panbronchiolitis with ground glass opacities. Both cases showed hypoxia, a high titer of serum anti-Tricosporon antibody and exacerbation in their own homes. Video-assisted thoracoscopic lung biopsy revealed granuloma in the bronchioles area. We diagnosed summer type hypersensitivity pneumonitis and this condition improved in response to antigen isolation and steroids. Remarkable changes in the bronchioles were characteristic in the two cases.

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ORIGINAL ARTICLE

Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis

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Prognostic value of circulating KL-6 in idiopathic pulmonary fibrosis
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Objective: Circulating levels of KL-6, a high MW glycoprotein (MUC1 mucin), are elevated in a majority of patients with a number of interstitial lung diseases, including idiopathic pulmonary fibrosis (IPF). However, KL-6 levels vary from patient to patient. The aim of the present study was to determine whether the serum KL-6 level at the time of diagnosis predicts prognosis in IPF.

Methods: The relationship between clinical variables and prognosis in 27 patients with IPF were analysed retrospectively. The diagnosis was made by histological examination ($n = 16$) or on clinical findings including high-resolution CT scanning ($n = 11$). All patients were followed up for at least 3 years. Variables such as age, FVC%, PaO_2 at rest, initial LDH level, C-reactive protein and KL-6 were used for analysis.

Results: At the cut-off level determined by receiver operating characteristic curves, LDH and KL-6 showed a significant correlation with the patient's prognosis by univariate analysis. However, multivariate analysis revealed that only KL-6 was a predictor of prognosis. The patients were categorized by their serum KL-6 levels (as above or below the cut-off level of 1000 U/mL) and their survival estimated using the Kaplan–Meier method. The difference in median survival between the two groups was significant. The median survival of patients with low KL-6 was more than 36 months, whereas that of patients with high KL-6 was only 18 months.

Conclusion: These results suggest that initial evaluation of serum KL-6 level can predict survival in patients with IPF.

Key words: idiopathic pulmonary fibrosis, MUC1, mucin, prognosis.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a form of idiopathic interstitial pneumonia characterized by progressive lung fibrosis and poor prognosis. Predicting survival in patients with IPF is difficult. In general, younger age, female, shorter symptomatic period prior to diagnosis, less dyspnoea, preserved pulmonary function, extent of ground-glass and reticular opacities on high-resolution CT (HRCT) scans, lymphocytosis (>20–25%) in BAL fluid and better

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response to treatment have been shown to be associated with longer survival.[1–5] Recently, a revised clinical-radiological-physiological scoring system for predicting survival time in IPF was reported by King *et al.*[6] There are seven variables in this scoring system including age, smoking status, finger clubbing, radiological findings of perfusion defects or pulmonary hypertension, TLC, and PaO_2 at maximal exercise. However, there is no validated serum marker for predicting prognosis.

A circulating high MW mucin-like glycoprotein, KL-6, which had been classified as human MUC1 mucin, has been identified.[7] KL-6 has been reported to be a sensitive marker for interstitial lung diseases, such as IPF, collagen vascular disease-associated interstitial pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, pulmonary sarcoidosis and pulmonary alveolar proteinosis.[8–11] Furthermore, serial measurements of serum KL-6 can predict the short-term prognosis following high-dose steroid therapy in patients with rapidly progressive IPF.[12] KL-6 can also predict the prognosis for particular types of drug-induced lung injury such as those associated with diffuse alveolar damage and chronic interstitial pneumonia patterns.[13] In patients with IPF, the range of values for circulating KL-6 is wide, ranging from normal to extremely high. Previous studies have suggested that a higher level of serum KL-6 is associated with active interstitial pneumonitis.[8] However, the significance of KL-6 level and predicting prognosis in IPF is not known.

Patients with IPF were carefully selected using the recently described classification of idiopathic interstitial pneumonias,[14] and the merit of using initial levels of serum markers such as KL-6 to determine the prognosis of IPF was investigated.

METHODS

Subjects

In total, 27 patients with IPF were assessed retrospectively. They were selected from 87 patients with idiopathic interstitial pneumonia obtained from pulmonologists at seven university hospitals (Hokkaido University, Fukui Medical University, Jichi Medical University, Kumamoto University, Ehime University, Kawasaki Medical University and Hiroshima University). Some patients had been assessed previously in a study of the utility of an assay for KL-6 (ED046, Sanko Junyaku, Tokyo, Japan).[15] Patients with interstitial pneumonitis of known aetiology were excluded. In total, 27 patients were selected on the basis of the following inclusion criteria: (i) data for %VC, arterial PaO_2 at rest, KL-6, C-reactive protein and LDH being available within 3 years of the onset of disease symptoms and before initiation of any specific treatment. The time between their initial visit and data collection was <6 months and all data were obtained within 1 month of the KL-6 measurement; (ii) follow-up data were available for at least 3 years; (iii) all patients had biopsy-proven or clinically diagnosed IPF and none of the patients was considered in rapid clinical progression at the time the data were obtained; and (iv) all were alive or alternatively had died of respiratory failure due to deterioration of IPF at the end of a follow-up period of 3 years. In order to assess the predictive value of KL-6 on mortality from IPF, patients who died from non-respiratory causes were excluded.

Among the patients, 19 were men and their mean age was 59 ± 10 years. There were 16 patients with biopsy-proven usual interstitial pneumonitis. The criteria used to diagnose the clinical IPF group ($n = 11$) were based on the typical findings of IPF such as honeycombing and traction bronchiectasis on HRCT.[5,16,17] Lung function tests were conducted according to the American Thoracic Society guidelines published in 1991,[18] using automatic spirometers (Chest, Tokyo, Japan). The formula by Baldwin was used to predict VC.[19] Ten patients died during the 3-year observation.

Measurement of serum markers

Serum KL-6 was measured by a sandwich ELISA, as described previously.[15] Previous studies had validated this assay: the intra-assay variation of KL-6 was satisfactory (coefficient of variation = 0.7–7.8%). The inter-assay coefficient of variation was 6.3–6.9%. This assay was not influenced by haemolysis (less than 10 g/L of Hb), chylomicron, or bilirubin (less than 5 g/L). Plasma LDH was measured in each hospital and normalized to a cut-off value of 400 IU/L.

Statistical analysis

All analyses were performed using StatView software, version 5.0.1 (SAS Institute, Cary, NC, USA). To find an optimal cut-off level, that is, the level that can discriminate survivors from non-survivors, receiver operating characteristics (ROC) curves were used. Univariate analyses were performed using logistic regression to identify significant variables predicting survival status. Variables that were significant by univariate analyses were taken as potential predictors of survival and were used as covariates in the multivariate logistic regression analysis to identify independent predictors of survival. Odds ratios, adjusted odds ratios and 95% confidence intervals were computed for variables. Age and the time interval between serum markers measurement and estimated onset of the disease were compared between patients with KL-6 values of ≥1000 and those with KL-6 values of <1000 by using a non-paired *t*-test. The survival function was estimated using the Kaplan–Meier method, and comparison was made using the log rank test. Significance was accepted when $P < 0.05$.

RESULTS

During the 3 years of observation, 10 of 27 patients died. To find an optimal cut-off level that could discriminate survivors from non-survivors, ROC curves were plotted. According to ROC curves, the cut-off levels for age, LDH, C-reactive protein and KL-6 were

Table 1 Analysis by receiver operating characteristic curves of age, %VC, PaO_2 and circulating markers to discriminate survivors from non-survivors in patients with idiopathic pulmonary fibrosis

Variables	AUC	Cut-off level	Sensitivity	Specificity	Accuracy
Age (years)	0.600	60	70.0	58.8	63.0
%VC (%)	0.571	70	70.6	60.0	66.7
PaO_2 (Torr)	0.647	75	58.8	60.0	59.3
KL-6 (U/mL)	0.800	1000	90.0	70.6	77.8
CRP (mg/dL)	0.603	0.65	50.0	76.5	66.7
LDH (IU/L)	0.700	550	70.0	76.5	74.1

AUC, area under the curve; CRP, C-reactive protein.

Table 2 Correlation between variables and survival in patients with idiopathic pulmonary fibrosis

Variables	Cut-off level	Odds ratio	95% confidence interval Lower	Upper	*P*-value
Univariate analysis					
Age (years)	60	3.33	0.632	17.57	0.156
%VC (%)	70	3.60	0.698	18.56	0.126
PaO_2 (Torr)	75	2.14	0.436	10.53	0.348
KL-6 (U/mL)	1000	16.50	1.666	163.50	0.017
CRP (mg/dL)	0.65	3.75	0.662	21.26	0.135
LDH (IU/L)	550	5.60	1.015	30.91	0.048
Multivariate analysis					
KL-6 (U/mL)	1000	12.56	1.195	131.90	0.035
LDH (IU/L)	550	3.59	0.520	24.76	0.195

CRP, C-reactive protein.

as shown in Table 1. Among the six variables, KL-6 had the highest diagnostic accuracy at these cut-off levels (77.8% vs. 63.0%, 66.7%, 59.3%, 66.7% and 74.1%, for age, VC% predicted, PaO_2, C-reactive protein and LDH, respectively). The results of univariate logistic correlation analysis are shown in Table 2. Both KL-6 and LDH had significant correlations with survival. However, multivariate analysis revealed that KL-6 but not LDH predicted prognosis (Table 2). Survival in patients with a KL-6 level above or below 1000 U/mL was estimated using the Kaplan–Meier method, and the survival was significantly different between the two groups (Fig. 1).

Age and the time lag between measuring serum markers and estimated onset of IPF were not different between patients with KL-6 value of ≥1000 U/mL and those with KL-6 value of <1000 U/mL (59.1 ± 10.4 vs. 59.0 ± 10.3 years, $P = 0.97$; 418 ± 336 vs. 465 ± 354 days, $P = 0.73$, respectively).

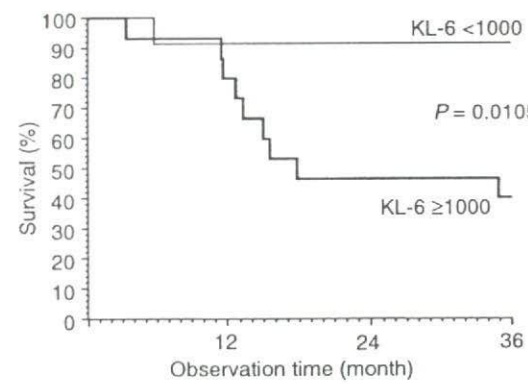

Figure 1 The survival function of KL-6 at the cut-off level of 1000 U/mL was estimated using the Kaplan–Meier method. The idiopathic pulmonary fibrosis patients with KL-6 levels less than 1000 ($n = 12$) showed significantly more favourable prognosis than those with a KL-6 level of 1000 U/mL or more.

DISCUSSION

This study suggests that the initial serum KL-6 level can predict prognosis of IPF. The ROC curves supported an initial KL-6 level of 1000 U/mL being the optimal cut-off point for discriminating between survivors and non-survivors during the 3-year follow-up observation. The curves also indicated that KL-6 was the best of the six indicators evaluated. A serum level of KL-6 lower than 1000 U/mL at the time of diagnosis predicts a better prognosis: with a more favourable 3-year survival rate, compared with patients with a KL-6 level ≥1000 U/mL.

Because outcome varies among the different histological subsets of idiopathic interstitial pneumonitis, the authors carefully selected patients with IPF. Age and %VC have previously been shown to be significant survival factors for IPF.[6] However, these were not

significant in the present study. Furthermore, there was no difference in age between the patients with KL-6 ≥1000 and <1000 U/mL. A decrease in the VC% predicted was associated with progression of the disease. As the authors selected patients who were within 3 years of the onset of their disease symptoms, the patients' lung function was largely preserved. Smoking status, which seems to be another factor, was not considered in the present study. However, circulating levels of KL-6 are not significantly influenced by smoking status,[20] indicating that KL-6 is likely to be an independent prognostic factor.

LDH but not C-reactive protein was significantly associated with survival in univariate analysis. C-reactive protein is an acute phase protein and is usually mildly elevated in IFP. However, recent studies suggest that alveolar epithelial damage rather than lung inflammation directly results in lung fibrosis.[21] This may explain why conventional therapy with corticosteroids and cytotoxic agents is ineffective. LDH may reflect lung cell damage,[22] although cell destruction in organs other than the lungs, such as liver and muscle, may influence the LDH level. Although serum KL-6 levels are significantly correlated with plasma total LDH activity,[15] multivariate analysis showed that KL-6 alone was an independent predictor for survival of IPF patients.

There are a few non-invasive indicators for prognosis of IPF.[23,24] Surfactant protein-A (SP-A) and SP-D are known to be such markers. Lung production of SP-A is reduced in IPF. Its concentration referenced to total phospholipids (SP-A/PL) in BAL fluid is significantly decreased in IPF patients compared with healthy volunteers, and in patients who died within 2 years of diagnosis compared with those who survive.[23] Furthermore, serum levels of SP-A and SP-D are significantly increased in non-survivors relative to those in survivors.[24] These are protein secretory products of the alveolar type II epithelial cells, and contribute to the function and metabolism of pulmonary surface-active material.

The exact reason why serum KL-6 can predict prognosis is unclear at present. The primary cellular source of KL-6 is also the type II pneumocytes.[8] KL-6 was located by immunohistochemistry in the epithelial cells of the pancreatic and mammary ducts, as well as in type II epithelial cells of the lung.[7] Circulating KL-6 decreased by approximately 35% following lobectomy, suggesting that a significant proportion of the circulating KL-6 is derived from the lung.[25] Furthermore, the concentration of KL-6 is estimated to be extremely high in the epithelial lining fluid of IPF patients, which is in striking contrast to the concentrations of SPs.[26] Such a fundamental difference may indicate a different role, although circulating levels of KL-6 are significantly correlated with those of SP-A or SP-D in patients with IPF.[27] An increase of circulating KL-6 in interstitial pneumonitis is thought to be due to an increase of KL-6 production by regenerating alveolar type II pneumocytes, and/or to enhanced permeability following destruction of the air–blood barrier in the affected lungs.[26,28] Increased diethylenetriamine penta-acetic acid clearance, which is an index of lung epithelial permeability, may be a sensitive marker of inflammation and predict poor survival in patients with IPF.[29] The ability to reflect such increased permeability may explain how serum levels of KL-6 predicts prognosis in IPF.

The present study has several limitations. This study included a small number of IPF patients and the diagnosis was histologically confirmed only in 60% of the patients. The smoking status, detailed HRCT findings and results of exercise tests were not obtained. Inclusion of these parameters and comparison with clinical, radiological and physiological scoring system[6] would be needed to establish the clinical value of KL-6 measurement in predicting prognosis in patients with IPF. It would also be interesting to determine whether serial measurement of KL-6 would be beneficial in predicting the prognosis among patients with IPF. A large, prospective study is warranted to confirm the observations in this retrospective report.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Significance of Serum Uric Acid in Patients with Chronic Respiratory Failure Treated with Non-invasive Positive Pressure Ventilation

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Abstract

Purpose The aim of the study was to evaluate serum uric acid (UA) levels before and after non-invasive positive pressure ventilation (NPPV) to assess the utility of serum UA as an indicator of acute exacerbation of chronic respiratory failure (CRF) in patients treated with NPPV.

Methods We analyzed change in the serum UA level in 29 patients with CRF due to restrictive thoracic disease and treated with NPPV.

Results After NPPV therapy, PaO_2 was significantly increased and $PaCO_2$ was significantly decreased in all patients. Sixty-two percent of patients (18 of 29) showed a decreased serum UA/creatinine (Cr) ratio after NPPV therapy, but, overall, there was no significant change in serum UA/Cr (P=0.0688). The change in serum UA/Cr was not correlated with the changes in PaO_2 and $PaCO_2$ after NPPV. When we compared patients in whom serum UA/Cr decreased (n=18) with patients in whom serum UA/Cr did not decrease (n=11), there were significantly fewer patients who suffered CRF exacerbation in the group with a decrease (P=0.0021). Furthermore, the cumulative proportion (Kaplan-Meier) of patients who did not suffer exacerbation of CRF was significantly higher in the group in which serum UA/Cr decreased (P=0.0003).

Conclusions Our data suggest that serum UA may be a useful clinical indicator of CRF exacerbation in patients treated by NPPV.

Key words: serum uric acid, chronic respiratory failure, non-invasive positive pressure ventilation, exacerbation

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Introduction

Continuous nocturnal oxygen desaturation due to sleep-associated hypoventilation results in daytime hypoxemia and hypercapnia in patients with chronic respiratory failure (CRF) (1). A possible sequela of sleep-associated hypoxemia is tissue hypoxia (2). Hypoxic conditions trigger a purine degradation cascade (3-5). Increased plasma levels and excretion of purine metabolites have also been observed in exercising human subjects (6) and in critically ill patients (7) under conditions of hypoxia and ischemia. Serum adenosine, a purine metabolite, may be a more sensitive marker of tissue hypoxia than uric acid (UA). However, the measurement of adenosine is technically difficult because of its short half-life in plasma (8). Consequently, UA is widely used as a clinical marker of tissue hypoxia because it is not metabolized further, and it is easy to sample and inexpensive to as-

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sess (9).

Serum and urinary UA are reported to be useful markers reflecting hypoxia in patients with various diseases such as obstructive sleep apnea syndrome (OSAS) (2, 8-11), chronic obstructive pulmonary disease (COPD) (9, 12, 13), chronic heart failure (14, 15), primary pulmonary hypertension (16), cyanotic congenital heart disease (17), and Eisenmenger syndrome (18). The therapeutic effects of oxygen and nasal continuous positive airway pressure (nCPAP) on UA excretion in hypoxemic patients have been examined. Oxygen therapy markedly reduced excretion of urinary UA in COPD patients (12). Additionally, several studies showed that overnight use of nCPAP reduced the urinary UA/creatinine ratio (UA/Cr) in OSAS patients (8-11).

Efficacy of long-term non-invasive positive pressure ventilation (NPPV) in patients with CRF has been reported (19). In general, NPPV acts by relieving respiratory muscle fatigue, improving respiratory system compliance by reversing microatelectasis of the lung, and lowering the respiratory center "set point" for CO_2 by ameliorating chronic hypoventilation (19). Chronic NPPV is effective for ventilatory failure due to restrictive thoracic disease (RTD) such as pulmonary tuberculosis sequelae (PTS), kyphoscoliosis (KS), or neuromuscular disease (19, 20). NPPV is widely used for patients with hypercapnic hypoxemic respiratory insufficiency. However, little is known about the effect of NPPV on tissue hypoxia and the clinical importance of serum UA in patients with CRF receiving NPPV. We hypothesized that long-term NPPV in patients with CRF would improve hypoventilation and tissue hypoxia, leading to a decrease in serum UA.

We conducted a preliminary study comparing serum UA levels before and after NPPV therapy to assess the utility of serum UA as an indicator of acute exacerbation of CRF in patients treated with NPPV.

Patients and Methods

Study subjects

Data were collected from patients with CRF due to RTD (PTS or KS) who were prescribed chronic NPPV therapy at one of our institutions during the 6-year period 1999-2005. The clinical data of 29 patients were retrospectively analyzed. All 29 patients met the criteria for hypercapnic respiratory failure ($PaCO_2 \geq 45$ mmHg in room air) (21). PTS was defined as severe restrictive pulmonary dysfunction with or without cor pulmonale due to previous *M. tuberculosis* infection involving the chest wall and lung parenchyma and/or pleura (22). KS was defined as a Cobb angle of >50° (23).

All patients met the selection guidelines for long-term non-invasive ventilation for RTD, as previously reported (19). In brief, all patients showed typical symptoms such as morning headaches, daytime hypersomnolence, energy loss, and impaired gas exchange attributable to chronic daytime and sustained nocturnal hypoventilation (19). Before NPPV therapy, all study patients were in clinically stable condition (no exacerbation of the CRF or hospital admission for at least 1 month prior to the study). No patient had rapidly progressive neuromuscular disease or obesity-hypoventilation syndrome. There was no evidence of renal dysfunction in any patient. Venous and arterial blood sampling was performed just before the start of NPPV therapy, and the resulting laboratory values were recorded as before-NPPV values. Venous and arterial blood samples were obtained again at least 10 months after NPPV, and resulting values were recorded as after-NPPV values.

Blood sampling for UA measurement and arterial blood gas (ABG) analysis

For measurement of serum UA and Cr, venous blood was obtained after an overnight fast. Serum UA and Cr levels were determined by the uricase-peroxidase method and creatinase-peroxydase method, respectively (24). Arterial blood samples were obtained from the brachial or femoral artery with patients in a supine position breathing room air or receiving supplemental oxygen. Arterial blood samples were obtained after NPPV therapy under these same conditions. The UA/Cr was calculated to adjust for kidney function, as previously reported (8-11, 25).

Measurement of change in serum UA (ΔUA/Cr)

ΔUA/Cr was calculated as described previously (2): ΔUA/Cr=100% × (UA/Cr after NPPV therapy−UA/Cr before NPPV therapy) ÷ UA/Cr before NPPV therapy.

NPPV

Bilevel NPPV was delivered via nasal or full face mask with a NIP nasal A (Teijin Pharma Limited, Tokyo, Japan) or CLEAN AIR EZ (Fukuda Denshi Co., Ltd., Tokyo, Japan) or BiPAP S/T (Fuji Respironics, Co., Ltd., Tokyo) ventilator. The commercial masks were of appropriate size to fit to each patient's nose or face. In 27 cases, the ventilator was set to spontaneous/timed mode at the maximal tolerated inspiratory positive airway pressure and at an expiratory positive airway pressure in the range of 3-6 cm H_2O, with a back-up respiratory rate below the awake spontaneous breathing rate. The ventilator was set to timed mode in the other two cases. Oxygen was supplied from the mask side port at a flow rate needed to achieve a target $SpO_2 \geq 90\%$.

Exacerbation of CRF

Exacerbation of CRF was defined as an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum to warrant a change in management (26) with uncompensated respiratory acidosis (pH<7.30) (27).

Comparison of patients with and without a decrease in serum UA

Patients were classified into two groups according to

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Table 1. Baseline Characteristics of Study Patients (n = 29)

Median age (yrs)		70 (54-81)
Sex ratio, male/female		14/15
Median BMI ($kg \cdot m^{-2}$)		18.1 (13.6-30.2)
H-J class	II	8
	III	10
	IV	11
PTS		25
KS		4
LTOT		25

BMI = body mass index, H-J class = Hugh-Jones classification, RTD = restrictive thoracic disease, PTS = pulmonary tuberculosis sequelae, KS = kyphoscoliosis, LTOT = long-term oxygen therapy

Number of patients is shown unless otherwise indicated.

For median values, ranges are shown in parentheses.

whether serum UA/Cr decreased after NPPV therapy: a UA/Cr decrease group and a non-UA/Cr decrease group.

Statistical analysis

Data are expressed as median values with ranges shown in parentheses. Differences between ABG values before and after NPPV therapy and between laboratory values before and after NPPV therapy were analyzed by Wilcoxon signed-rank test. Differences in baseline characteristics, in changes in ABG values, and in the number of CRF exacerbations between the UA/Cr decrease group and the non-UA/Cr decrease group were analyzed by Mann-Whitney U test. Spearman's rank correlation coefficient was used to examine correlation between variables. Differences between groups in the number of patients taking diuretics and in the number who suffered CRF exacerbation were analyzed by Fisher's exact test. The proportion of patients who did not suffer exacerbation of CRF in each of the two groups was derived by the Kaplan-Meier method and was compared by log-rank test. Statistical significance was accepted at $P<0.05$.

Results

Baseline characteristics of the study patients are shown in Table 1. Median age of the patients (14 men and 15 women) was 70 years (range, 54-81 years). Twenty-five patients had PTS, and 4 had KS. Patients were classified into three groups according to the degree of clinical breathlessness per Fletcher-Hugh-Jones classification (28): grade 2, n=8; grade 3, n=10, and grade 4, n=11. No patient was taking any medication such as alloprinol, a thiazide diuretic, or aspirin during the study, but 52% of patients (15 of 29) were taking a loop diuretic, and 24% (7 of 29) were taking theophylline. Body mass index was 18.1 (13.6-30.2) kg/m^2. Eighty-six percent of patients (25 of 29) had received long-term oxygen therapy (LTOT) before NPPV therapy. Indices of lung function obtained before the study were as follows: vital capacity (VC) 1.00 (0.47-2.11) L (percentage of predicted value 38.1 (21.6-58.6)), $FEV_{1.0}$ 0.59 (0.34-1.13) L, and $FEV_{1.0}/VC$ 63.4 (38.9-101.3)%. Median daily use of the ventilator for all patients was 7 hours (range, 6-10 hours).

ABG and laboratory values before and after NPPV are shown in Table 2. The NPPV treatment period was 15 (11-24) months. The pH did not change after NPPV therapy. Overall, PaO_2 was significantly higher after NPPV therapy than before NPPV therapy ($P<0.0001$). In addition, $PaCO_2$ decreased significantly after NPPV therapy ($P=0.0003$). There were no significant changes in serum creatinine, total protein, albumin, and hemoglobin levels after NPPV therapy.

As shown in Fig. 1, 62% of patients (18 of 29) showed a decrease in serum UA/Cr after NPPV therapy, but, overall, there was no significant change in serum UA/Cr ($P=0.0688$). ΔUA/Cr did not correlate with the changes in PaO_2 (ΔO_2) and $PaCO_2$ (ΔCO_2) after NPPV (Fig. 2). Characteristics of the two groups (UA/Cr decrease group and non-UA/Cr decrease group) are shown in Table 3. There were no significant differences in baseline characteristics including age, body mass index (BMI), serum Cr, total protein, albumin, hemoglobin, lung function, and ABG values between the two groups. There was no significant difference in NPPV use such as daily use of the ventilator or the treatment period. Moreover, there was no significant difference in change in BMI, body weight, or any parameter of metabolism. In addition, there was no statistical difference between the two groups in ΔO_2 or ΔCO_2. In the UA/Cr decrease group, 3 of 18 patients suffered CRF exacerbation, whereas in the non-UA/Cr decrease group, 9 of 11 patients suffered CRF exacerbation ($P=0.0021$). The cumulative proportion of patients who did not suffer exacerbation of CRF in each of the two study groups is shown in Fig. 3. The proportion was significantly higher in the UA/Cr decrease group than in the non-UA/Cr decrease group ($P=0.0003$).

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Table 2. Arterial Blood Gas and Laboratory Values before and after NPPV

	Before NPPV	After NPPV	*P* value
Arterial blood gas			
pH	7.37 (7.31-7.45)	7.38 (7.33-7.47)	0.3810
PaO_2 (mmHg)	65.3 (39.9-100.2)	76.1 (51.9-106.3)	< 0.0001
$PaCO_2$ (mmHg)	66.2 (53.6-102.2)	61.6 (46.1-92.5)	0.0003
Laboratory			
Creatinine (mg/dl)	0.6 (0.1-0.9)	0.6 (0.2-1.1)	0.5014
Total protein (g/dl)	7.1 (5.5-9.0)	7.0 (5.8-8.6)	0.8987
Albumin (g/dl)	4.1 (3.1-4.7)	4.1 (2.6-5.0)	0.9610
Hemoglobin (g/dl)	12.4 (9.6-15.3)	12.3 (9.4-15.8)	0.1275

P values obtained by Wilcoxon test.

Data are shown as median values, with ranges in parentheses.

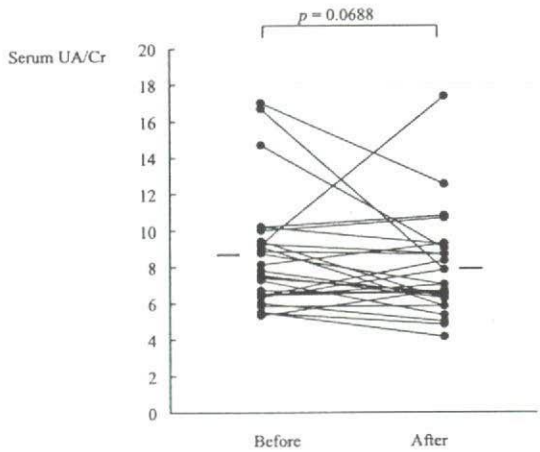

Figure 1. Serum UA levels before and after treatment with NPPV. Serum UA did not change significantly after NPPV therapy ($P = 0.0688$). UA = uric acid; Before = before NPPV therapy; After = after NPPV therapy. *P* value obtained by Wilcoxin test.

Discussion

In the present study, long-term NPPV therapy improved hypoventilation. Sixty-two percent of patients (18 of 29) showed a decreased serum UA/Cr, but, overall, there was no significant change in serum UA/Cr after NPPV therapy. There was no significant correlation between ΔUA/Cr and changes in blood gas values. When patients were classified into two groups according to the change in serum UA/Cr, there were significantly fewer patients who suffered CRF exacerbation in the UA/Cr decrease group than in the non-UA/Cr decrease group. The cumulative proportion of patients who did not suffer CRF exacerbation was significantly higher in the UA/Cr decrease group than in the non-UA/Cr decrease group.

Previous studies have shown that improved oxygenation leads to a decrease in UA (8-12). Basal urinary excretion of adenosine triphosphate catabolic products including UA has been shown to be significantly greater in severely hypoxemic COPD patients than in control patients and to be significantly decreased after oxygen therapy (12). Moreover, in OSAS patients, a significant increase in the UA/Cr has been observed in association with nocturnal hypoxia; nCPAP treatment led to a significant reduction in this ratio (8-11). NPPV therapy, for which compliance was quite excellent, markedly improved the ventilatory state and oxygen supply in our study patients. We hypothesized that long-term NPPV would improve hypoventilation and tissue hypoxia, leading to a decrease in serum UA/Cr. Our results showed that serum UA/Cr tended to decrease after NPPV therapy. However, we failed to show significant correlation between ΔUA/Cr and changes in blood gas values. Previous studies have failed to show a strict relation between ΔUA/Cr and several markers such as the desaturation score, the nadir of arterial oxyhemoglobin desaturation, and daytime blood gas values in patients with OSAS who underwent overnight CPAP therapy (2, 9, 11). Sato et al showed a negative correlation between the ΔUA/Cr and minimum SpO_2 in COPD patients receiving LTOT. Why did we fail to find a correlation between ΔUA/Cr and ΔO_2? The possible explanations are as follows: the level of hypoxemia alone may not predict the presence of tissue hypoxia. Tissue hypoxia indicates inadequate oxygen supply against oxygen demand in the integrity of cellular metabolic processes (29). Oxygen delivery to the periphery is determined by two major factors: oxygen content of arterial blood, which is calculated by the hemoglobin concentration, SaO_2, and PaO_2, and the amount of blood flow, i.e., cardiac output (29). Other factors such as the oxyhemoglobin dissociation curve and pH also influence oxygen delivery. Thus, levels of PaO_2 correlate poorly with tissue hypoxia (9). In addition, improvement of pulmonary hypertension leads to a decrease in serum UA. Serum UA levels decreased in association with a reduction in total pul-

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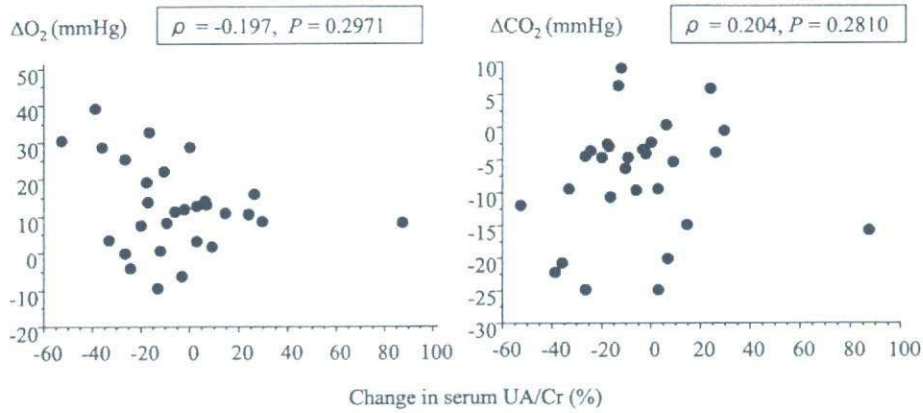

Figure 2. Correlation between ΔUA and changes in blood gas values. ΔUA = 100% × (serum UA after NPPV therapy- serum UA before NPPV therapy)/ serum UA before NPPV therapy; ΔO_2 = PaO_2 after NPPV therapy -PaO_2 before NPPV therapy; ΔCO_2 = $PaCO_2$ after NPPV therapy -$PaCO_2$ before NPPV therapy. *P* value obtained by Spearman's rank correlation coefficient.

Table 3. Baseline Characteristics, ABG Changes, and Number of Patients who Suffered CRF Exacerbation in the Two Study Groups

	UA/Cr decrease (n=18)	non-UA/Cr decrease (n=11)	*P* value
Baseline characteristics			
Age (years)	70 (58-80)	71 (54-81)	0.8573
BMI ($kg \cdot m^{-2}$)	18.1 (14.2-28.2)	15.6 (13.6-30.2)	0.9641
Diuretics/ no diuretics			
(no. of patients)	9/9	7/4	0.7301*
Creatinine (mg/dl)	0.6 (0.1-0.9)	0.6 (0.4-0.9)	0.1635
Total protein (g/dl)	7.1 (5.5-9.0)	6.9 (5.9-7.4)	0.2112
Albumin (g/dl)	4.1 (3.1-4.7)	4.1 (3.6-4.3)	0.4539
Hemoglobin (g/dl)	12.9 (10.6-15.3)	12.4 (9.6-13.8)	0.2484
VC (L)	0.97 (0.47-2.06)	1.16 (0.68-2.11)	0.0532
%VC (%)	35.0 (21.6-56.0)	42.1 (25.4-58.6)	0.1514
$FEV_{1.0}$(L)	0.55 (0.34-1.13)	0.82 (0.36-1.04)	0.2487
pH	7.37 (7.33-7.45)	7.37 (7.30-7.43)	0.9641
PaO_2 (mmHg)	64.0 (39.9-100.2)	70.0 (46.2-81.9)	0.8573
$PaCO_2$ (mmHg)	64.4 (55.4-102.2)	69.2 (53.6-101.1)	0.6531
ABG changes			
ΔO_2 (mmHg)	11.8 (-9.4-39.3)	10.9 (1.7-29.0)	> 0.9999
ΔCO_2 (mmHg)	-4.5 (-24.7- -1.2)	-5.3 (-24.8-6.1)	> 0.9999
Treatment period (months)	15 (12-24)	16 (11-23)	0.8220
Daily ventilator use (hours)	7 (6-10)	7 (6-9)	0.2644
Exacerbation/No exacerbation			
(no. of patients)	3/15	9/2	0.0021*

ABG = arterial blood gas analysis, CRF = chronic respiratory failure, VC = vital capacity, $FEV_{1.0}$ = forced expiratory volume in 1 second, ΔO_2 = PaO_2 after NPPV therapy-PaO_2 before NPPV therapy, ΔCO_2 = $PaCO_2$ after NPPV therapy - $PaCO_2$ before NPPV therapy.

P values obtained by Mann-Whitney U test no less than otherwise indicated. Data are shown as median values, with ranges in parenthesis.

* by Fisher's exact test.

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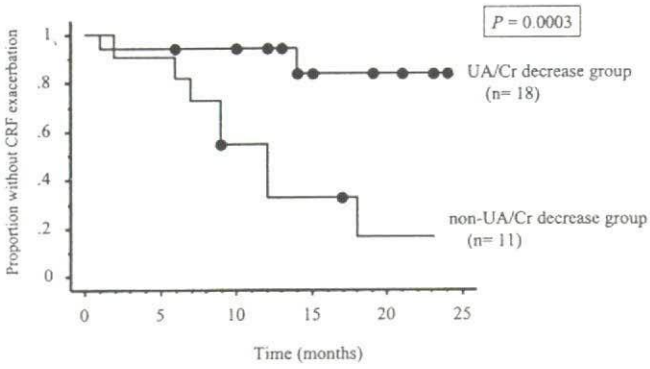

Figure 3. **Kaplan-Meier plot showing the proportion of patients without exacerbation of CRF in each of the two study groups. The UA decrease group had a significantly higher proportion of patients who did not suffer exacerbation of CRF than the non-UA decrease group had (P=0.0003 by log rank test). CRF= chronic respiratory failure.**

monary resistance during vasodilator therapy in patients with primary pulmonary hypertension (16). In patients with RTD, long-term NPPV therapy reportedly improved pulmonary hemodynamics (30, 31). Lack of improvement in pulmonary hypertension may lead to lack of a decrease in UA in some patients. Finally, lack of a significant relation between ΔUA/Cr and ΔO_2 might have been due simply to the small sample group.

Serum UA may be a useful clinical marker for exacerbation of CRF in patients with RTD. Previous studies have shown that serum UA increases in proportion to the severity of heart failure (15, 16) and that it is a strong prognostic marker in patients with chronic heart failure (14, 15), primary pulmonary hypertension (16), and Eisenmenger syndrome (18). Concerning CRF, Sato et al reported that ΔUA/Cr is a reliable indicator of prognosis in COPD patients receiving LTOT (13). However, there has been no report of the clinical significance of serum UA/Cr in RTD patients. In the present study, significantly fewer RTD patients who showed a decrease in serum UA/Cr (versus those who did not show a decrease) suffered CRF exacerbation. Furthermore, the cumulative proportion of patients without exacerbation of CRF was significantly higher in the UA/Cr decrease group than in the non-UA/Cr decrease group. Thus, our data suggest that UA/Cr is a valuable predictor of CRF exacerbation in RTD patients treated by NPPV. Why did such patients not show a decrease in serum UA/Cr despite the improved oxygenation? As noted above, the difference in the extent of improvement in pulmonary hemodynamics, SaO_2, the oxyhemoglobin dissociation curve, and pH may have influenced on the proportion of patients with CRF exacerbation in the two groups.

Mention should be made of the study limitations. First, diuretics, theophylline, digitalis, and aspirin are known to affect serum UA metabolism (2, 9). In this study, 52% of patients (15 of 29) were taking loop diuretics, and 24% of patients (7 of 29) were taking theophylline. Thus, we did not change any medical treatment, such as diuretics and theophylline, and we compared laboratory data including ABG values before and after NPPV therapy. Second, the treatment period varied from 11 to 24 months. However, there was no significant difference in the treatment period between the UA decrease group and the non-UA decrease group. Further study in a large number of patients may confirm the usefulness of this simple, inexpensive test for periodic follow-up of patients with CRF receiving NPPV.

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