TECHNICAL REPORT
RERF TR 6-88
業 績 報 告 書

A NEW SERUM INDICATOR OF ACTIVITY OF INTERSTITIAL PNEUMONITIS: SIALYLATED CARBOHYDRATE ANTIGEN KL-6

間質性肺炎の活動性を表す血清中の新しい指標 シアル化糖鎖抗原 KL-6

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ACKNOWLEDGMENT
謝　辞

The authors gratefully acknowledge the excellent technical assistance of Kyoko Ozaki, Yoshiko Watanabe, Yoko Mizunoe, and Tomoko Hokao. We also wish to thank Professor Shoji Tokuoka, the Second Department of Pathology, Hiroshima University School of Medicine, for providing tissue specimens, and Dr. Masao Kuwabara, Hiroshima Prefectural Hospital; Dr. Hiroshi Fukuda, Mizushima Kyodo Hospital; Dr. Hiroya Egawa, Asa City Hospital; Dr. Mikio Fujita, Yoshijima Hospital; and Dr. Shigeru Matsusaka, Tadanoumi Hospital for providing serum samples, and Dr. Michael A. Bean, Virginia Mason Research Center, for editing the manuscript.

多大なる技術援助をいただいた尾崎恭子，渡辺芳子，水之江容子並びに外尾智子の諸氏に対して深く謝意を表する．組織標本を御提供いただいた広島大学医学部第２病理学教室の徳岡昭治教授，血清試料を御提供いただいた県立広島病院の桑原正雄博士，水島協同病院の福田 博博士，安佐市民病院の江川博彌博士，吉島病院の藤田幹雄博士，忠海病院の松坂 茂博士に対して，また，原稿を御校閲いただいたVirginia Mason研究センターのDr. Michael A. Beanに対しても謝意を表する．

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The Radiation Effects Research Foundation (formerly ABCC) was established in April 1975 as a private nonprofit Japanese Foundation, supported equally by the Government of Japan through the Ministry of Health and Welfare, and the Government of the United States through the National Academy of Sciences under contract with the Department of Energy.

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放影研 RERF RADIATION EFFECTS RESEARCH FOUNDATION
財団法人 放射線影響研究所

Research Project 研究課題 16-81

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間質性肺炎の活動性を表す血清中の新しい指標 シアル化糖鎖抗原KL-6

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SUMMARY

Serum levels of a high molecular weight circulating antigen KL-6, which is detected by sandwich assay using a monoclonal antibody KL-6 against a sialylated carbohydrate antigen, were examined for usefulness in monitoring the activity of interstitial pneumonitis. Of the 59 interstitial pneumonitis patients, 34 (58%) exhibited abnormally high levels of KL-6 antigen in their sera and no significant correlation between serum KL-6 values and lactic dehydrogenase activities was noted. Moreover, KL-6 antigen levels showed a positive correlation with the degree of clinical activity of the disease as measured by ^{67}Ga-citrate scintigram and clinical outcome over time. These data suggest that serum KL-6 antigen may be a new useful indicator for estimating the degree of activity of interstitial pneumonitis, although it cannot be used for differential diagnosis of this disease from other malignant and nonmalignant diseases showing abnormally high levels of KL-6 antigen.

要 約

シアル化糖鎖抗原に対するモノクローナル抗体KL-6を使用するサンドイッチアッセイで検出される高分子量の循環抗原KL-6の血清中の値が，間質性肺炎の活動性を監視するために有用であるかどうかが検討された．59例の間質性肺炎患者のうち，34例（58%）が血清中にKL-6抗原の異常高値を呈したが，血清KL-6抗原値とLDH活性の間には有意の相関を認めなかった．更に，KL-6抗原値は，^{67}Ga-クエン酸シンチグラムや経過観察で測られた疾患の臨床的活動性の程度と正の相関を示した．これらのデータは，血清中KL-6抗原が異常高値を示す悪性あるいは非悪性の疾患から間質性肺炎を鑑別診断するためにその値を用いることはできないが，間質性肺炎の活動性の程度を推量するための新しい指標として血清KL-6抗原が有用であろうことを示唆している．

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Approved 承認 11 May 1988

Printed 印刷 September 1988

INTRODUCTION

Interstitial pneumonitis is a fatal disease of many different etiologies with histopathologically diffuse alveolar damage associated with infiltration of inflammatory cells in the interstitium and degeneration of pneumocytes and bronchiolar epithelia. In cases of hypersensitivity pneumonitis of known etiology, remission can be readily induced by removing the patient from the environment containing the antigen. However, since there is no effective therapy for interstitial lung diseases of unknown cause [idiopathic interstitial pneumonia (IIP)] except for adrenocortical hormones and immunosuppressive drugs which are occasionally effective,[1,2] the mean survival period is reported to be as short as 4.5 years by Turner-Warwick et al[3] and 7.5 years by Yamaoka et al.[4] It is therefore important for clinical treatment and care of the patients with the disease to precisely evaluate the degree of clinical activity of the disease.

However, there are only three kinds of examinations which are considered to be reliable in determining the clinical activity of IIP.[5] The first, open lung biopsy, is an invasive examination which sometimes can induce acute exacerbation. The second, ^{67}Ga-citrate scintigram, is possible only in hospitals which have the facilities for using radioisotopes. Frequent use of the scintigram in patient should be avoided due to the damage by radioactivity. The third, analysis of cell populations in bronchoalveolar lavage fluid, sometimes inflicts pain of patients. Since these examinations cannot be frequently performed on the same patient, new methods that are less traumatic and more convenient should be developed.

Lactic dehydrogenase (LDH) activity, circulating immune complexes (CIC), type III procollagen N-terminal peptides, and fibronectin have been investigated as circulating markers for evaluating the disease activity of interstitial pneumonitis. Though serum LDH activity is reported to occasionally increase during acute exacerbation of interstitial pneumonitis,[6] it is not a sensitive marker. Serum levels of CIC[7-10] and type III procollagen N-terminal peptides[11,12] have been reported to be useful for assessing clinical activity in IIP cases. However, CIC levels are difficult to evaluate, because values obtained for the same serum but with different assay methods can vary considerably. CIC levels are influenced by other conditions such as collagen diseases. Examination of the fibronectin

緒　言

間質性肺炎は多くの様々な病因から起こり，組織病理学的に見ると，間質への炎症細胞の浸潤及び肺胞細胞や細気管支上皮の変性を伴う瀰慢性肺胞損傷を示す致死性の疾患である．病因が判明している過敏性間質性肺炎の症例については，患者をその抗原を含む環境から遠ざけることにより容易に緩解が得られる．しかし，原因不明の間質性肺疾患〔特発性間質性肺炎（IIP）〕については，有効な場合もある副腎皮質ホルモンや免疫抑制剤[1,2]を除くと効果的な治療法がないため，平均生存期間は短く，Turner-Warwick ら[3]によれば4年半，山岡ら[4]によれば7年半である．したがって，本疾患の患者の臨床治療にあたっては，疾患の臨床的活動性の程度を正確に評価することが重要である．

しかし，IIP の臨床的活動性の決定において信頼できると考えられる検査法は，わずか3種類しかない．[5] 第一の開胸肺生検は観血性検査であり，ときに急性増悪を誘発し得る．第二の ^{67}Ga-クエン酸シンチグラムは，放射性同位元素取扱施設のある病院でのみ可能である．患者にシンチグラムを頻回使用することは，放射線障害を考慮し避けるべきである．第三の気管支肺胞の洗浄液中の細胞集団解析は，患者に苦痛を与えることがある．これらの検査を同一患者に頻繁に行うことはできないので，より侵襲性が低く，より便利な新しい方法を開発するべきである．

間質性肺炎の疾患活動性評価のための循環マーカーとして，乳酸脱水素酵素（LDH）活性，循環免疫複合体（CIC），Ⅲ型前膠原質N末端ペプチド，フィブロネクチンが検討されてきた．血清中の LDH 活性は間質性肺炎の急性増悪時にしばしば増加することが報告されているが，[6] 感度の高いマーカーではない．CIC[7-10] やⅢ型前膠原質N末端ペプチド[11,12] の血清中の濃度が，IIP 症例の臨床的活動性評価に有用であると報告されている．しかし CIC 濃度については，同一血清について得られた値であっても測定方法が異なると測定値がかなり変動し得るため，活動性の評価が困難である．CIC 濃度は膠原病のような他の病気によって影響を受ける．気管支肺胞洗浄液中のフィブロネクチン濃度検査は臨床的に有用であると

level in bronchoalveolar lavage fluid has been reported to be clinically useful, but its level in plasma is of little value as a parameter of clinical activity in interstitial pneumonitis.[13]

We have developed a monoclonal antibody KL-6 (IgG_1),[14] which recognizes a sialylated carbohydrate antigen on the high-molecular-weight mucin-like antigen (molecular weight >1,000 K), values of which increase at a high rate in the sera of interstitial pneumonitis patients. This antigen has also been found to be markedly increased in the sera of patients with pulmonary adenocarcinoma and tuberculosis.[14] This study describes the measurement of KL-6 antigen levels in sera as a potential indicator of disease activity in interstitial pneumonitis patients.

METHODS AND MATERIALS

Immunoperoxidase staining

The results of immunoperoxidase staining of frozen tissue sections with KL-6 monoclonal antibody have been reported previously.[15] In this report, the distribution of KL-6 antigen on formalin-fixed and paraffin-embedded tissues of normal lung and lung tissue exhibiting interstitial pneumonitis was examined. Immunoperoxidase staining using Vectastain (Vectar Laboratory, Burlingame, CA) was performed as previously reported.[15] In brief, the intrinsic peroxidase activity of tissues was inactivated by treatment with 0.3% H_2O_2 in methanol for 30 minutes after blocking nonspecific binding with horse serum. After washing, the specimens were reacted with 100-fold diluted KL-6 hybridoma culture supernatant at room temperature for 30 minutes. Culture supernatant of MOPC-21 cells, a mouse myeloma cell line secreting IgG_1 antibodies, was used as a negative control. After washing, sections were treated with biotinylated horse antimouse IgG for 30 minutes and then for one hour with avidin-biotin-conjugated horseradish peroxidase. The immunohistochemical reaction was developed for one hour with freshly prepared color development solution [0.5 mg/ml 3,3'-diaminobenzidine, tetrahydrochloride (Wako Fine Chemical, Japan), 0.01% H_2O_2, 50 mM Tris-HCl buffer pH 7.0]. After washing, the sections were counterstained with hematoxylin.

Quantification of KL-6 antigen in serum

Levels of KL-6 antigen in sera were quantified by sandwich-type enzyme-linked immunosorbent assay (ELISA) using KL-6 antibodies as previously

報告されているが，その血漿中の濃度は間質性肺炎の臨床的活動性のパラメーターとしてはほとんど価値がない.[13]

我々は，間質性肺炎患者の血清中で高率に上昇する高分子量のムチン様抗原（分子量＞1,000 K）上のシアル化糖鎖抗原を認識するモノクローナル抗体 KL-6（IgG_1）[14]を開発した．この抗原は肺腺癌や結核患者の血清中でも著しく増加することが発見されている.[14] 本研究では間質性肺炎患者の疾患活動性の有力な指標としての血清KL-6抗原値の測定について報告する．

方法及び材料

免疫ペルオキシダーゼ染色

KL-6モノクローナル抗体を用いての凍結組織切片の免疫ペルオキシダーゼ染色の結果については以前に報告している.[15] 今回の研究では，正常な肺と間質性肺炎の徴候のある肺のホルマリン固定パラフィン包埋組織上のKL-6抗原の分布について検討した．前回の研究[15]と同様，Vectastain（Vectar Laboratory, Burlingame, CA）を用いて免疫ペルオキシダーゼ染色を行った．要約すると，組織内在のペルオキシダーゼ活性を，ウマ血清で非特異結合を阻害後0.3% H_2O_2・メタノール溶液と30分間反応させて不活性化させた．標本を洗浄後，100倍希釈のKL-6ハイブリドーマ培養上澄と室温で30分間反応させた．IgG_1抗体を分泌するマウス骨髄腫細胞株であるMOPC-21細胞の培養上澄を陰性対照として用いた．切片を洗浄後，ビオチン化ウマ抗マウスIgGと30分間，次にアビジン・ビオチン標識西洋ワサビ・ペルオキシダーゼと1時間反応させた．この標本と新たに調製した発色溶液〔0.5 mg/ml 3，3′-diaminobenzidine, tetrahydrochloride（和光純薬，日本），0.01% H_2O_2，50 mM Tris-HCl 緩衝液pH 7.0〕との免疫組織化学反応を1時間，持続させた．切片を洗浄後，ヘマトキシリンで対比染色した．

血清KL-6抗原の定量

前回の報告[14]と同様，血清KL-6抗原値はKL-6抗体を用いて，サンドイッチ・タイプのenzyme-linked

reported.[14] In brief, polystyrene beads coated with KL-6 antibodies were incubated with 0.3 ml of 40-fold diluted serum at 37°C for three hours. After washing with 0.85% NaCl, 0.3 ml of 1,000-fold diluted horseradish peroxidase-conjugated KL-6 antibody was added and incubated at 37°C for 16 hours. After washing, the beads were transferred into a polystyrene tube. To the beads, 0.3 ml of OPDA solution (0.3% *o*-phenylenediamine dihydrochloride, 0.02% H_2O_2, 0.15 M citrate-phosphate buffer pH 4.9) was added and allowed to react at room temperature for 30 minutes. To the tube, 1.0 ml of 2 N HCl was then added to inhibit the peroxidase reaction and absorbance OD_{492} was measured. Pleural effusion from a lung cancer patient was serially diluted and used as standard reference in each assay.

RESULTS

Distribution of KL-6 antigens in the tissues of normal lung and lung exhibiting interstitial pneumonitis

Immunoperoxidase staining of normal lung tissues with KL-6 antibody showed that the antibody reacted strongly with type II pneumocytes and cells of the respiratory bronchiolar epithelium and weakly with basal cells of the terminal bronchiolar epithelium, a portion of middle layer cells of the bronchial epithelium and serous cells of the bronchial gland, but did not react with type I pneumocytes, goblet cells or mucous cells of the bronchial gland. The distribution of KL-6 antigens was different from those of sialomucin and sulfomucin stained by high iron diamine-alcian blue.

On the IIP lung sections, KL-6 antibodies reacted with regenerating type II pneumocytes and macrophages or type II pneumocytes present in air spaces, but not with interstitial components or hyalin membrane (Figure 1).

Levels of KL-6 antigen in sera

Figure 2 shows the levels of KL-6 antigen in sera of healthy controls and patients with nonmalignant diseases of the lung. As the level for 160 healthy controls was 258 ± 131 U/ml (mean ± SD), the cutoff point was set at 520 U/ml (mean + 2SD). The positive rates for nonmalignant diseases of the lung were 14% (3/21) for alveolar pneumonia, 0% (0/15) for chronic bronchitis, 11% (1/9) for bronchial asthma, 40% (4/10) for emphysema, 40% (2/5) for bronchiectasis, 43% (9/21) for pulmonary

immunosorbent assay (ELISA) により測定した．要約すると，KL-6抗体でコーティングしたポリスチレン・ビーズを40倍希釈血清0.3 ml と37℃で3時間反応させた．0.85% NaCl で洗浄後，1,000倍希釈の西洋ワサビ・ペルオキシダーゼ標識KL-6抗体0.3 ml を加え，37℃で16時間反応させた．これを洗浄後，ビーズをポリスチレン管に移した．ビーズに，0.3 ml のOPDA 溶液（0.3% *o*-phenylenediamine dihydrochloride，0.02% H_2O_2，0.15M クエン酸リン酸緩衝液 pH 4.9）を加え，室温で30分間反応させた．次にポリスチレン管に2 N HCl 1.0 ml を加えペルオキシダーゼ反応を停止させ，吸光度 OD_{492} を測定した．1人の肺癌患者の胸水を連続希釈し測定ごとの基準値として用いた．

結　果

正常肺組織と間質性肺炎の徴候を示す肺組織におけるKL-6抗原の分布

KL-6抗体を用いた正常肺組織の免疫ペルオキシダーゼ染色によると，KL-6抗体はII型肺胞細胞及び呼吸細気管支上皮の細胞とは強く反応し，終末細気管支上皮の基底細胞，気管支上皮の中間層細胞の一部及び気管支腺の漿液細胞とは弱く反応したが，I型肺胞細胞，杯細胞や気管支腺の粘液細胞とは反応しなかった．KL-6抗原の分布は，high iron diamine-alcian blue により染色された唾液ムチン質や硫酸ムチン質の分布とは異なっていた．

IIP の肺切片では，KL-6抗体は再生中のII型肺胞細胞やマクロファージ，又は気道空隙に存在するII型肺胞細胞と反応したが，間質成分や硝子膜とは反応しなかった（図1）．

血清中のKL-6抗原値

図2は健常対照者の血清と非悪性肺疾患患者の血清中のKL-6抗原値を示す．160人の健常対照者の値は258±131 U/ml（平均±SD）であったので，打ち切り値は520 U/ml（平均＋2 SD）とした．非悪性肺疾患における陽性率は各々，肺胞肺炎14%（3/21），慢性気管支炎0%（0/15），気管支喘息11%（1/9），肺気腫40%（4/10），気管支拡張症40%（2/5），

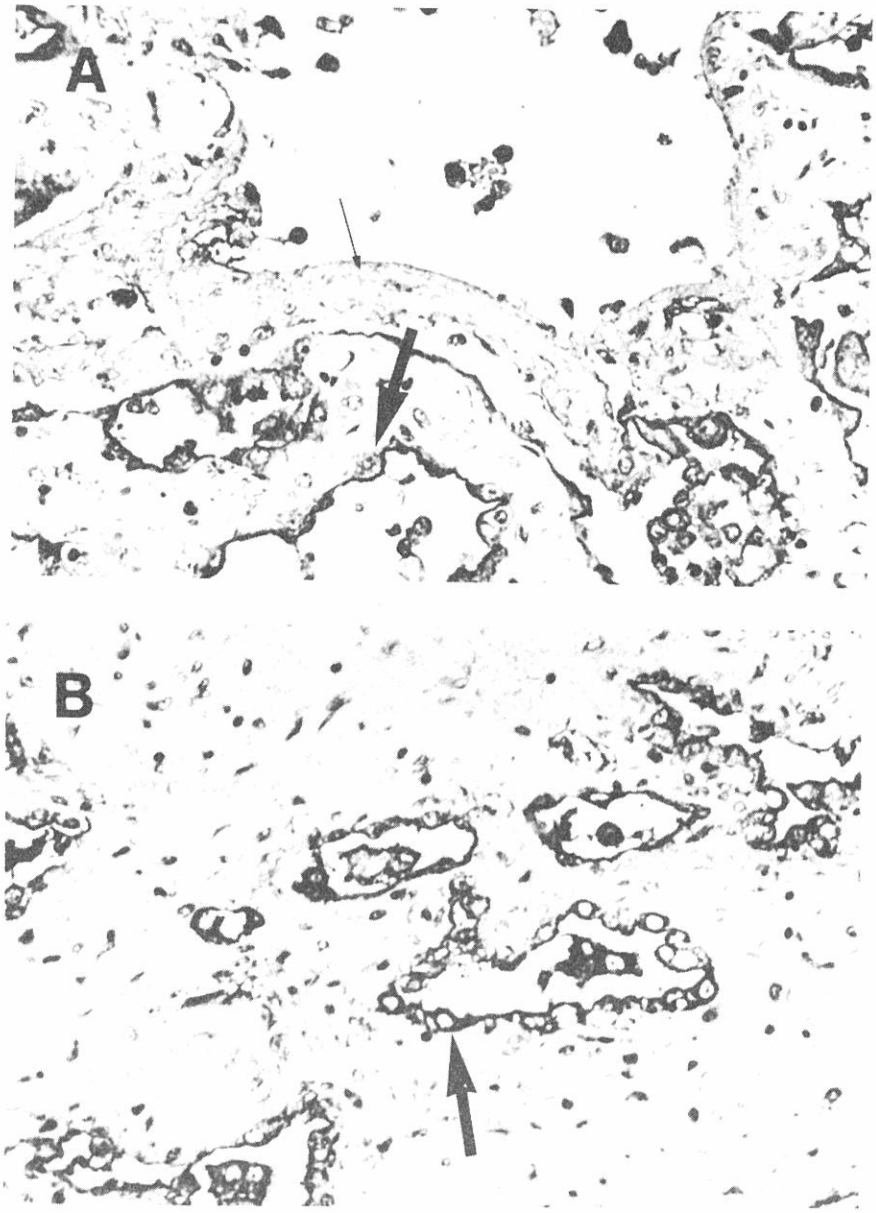

Figure 1. Distribution of KL-6 antigen on tissue from idiopathic interstitial pneumonitis patients was examined by immunoperoxidase staining (ABC method) and the sections were counterstained with hematoxylin. A) Section of lung tissue exhibiting acute pneumonitis; KL-6 antibodies reacted markedly with the apical region of regenerating type II pneumocytes (large arrow) but not with hyalin membrane (small arrow). B) Lung section of fibrotic change; KL-6 antibodies reacted strongly with regenerating type II pneumocytes (large arrow) and macrophages or type II pneumocytes existing in air spaces, but did not react with interstitial components.

図１．特発性間質性肺炎患者の組織のKL-６抗原の分布を免疫ペルオキシダーゼ染色（ABC法）により検討し，切片はヘマトキシリンで対比染色した．A）急性肺炎の徴候を示す肺組織の切片：KL-６抗体は再生中のⅡ型肺胞細胞の先端部と顕著に反応した（太い矢印）が，硝子膜とは反応しなかった（細い矢印）．B）肺切片の線維性病変：KL-６抗体は再生中のⅡ型肺胞細胞（太い矢印）やマクロファージ，又は気道空隙に存在するⅡ型肺胞細胞とは強く反応したが，間質成分とは反応しなかった．

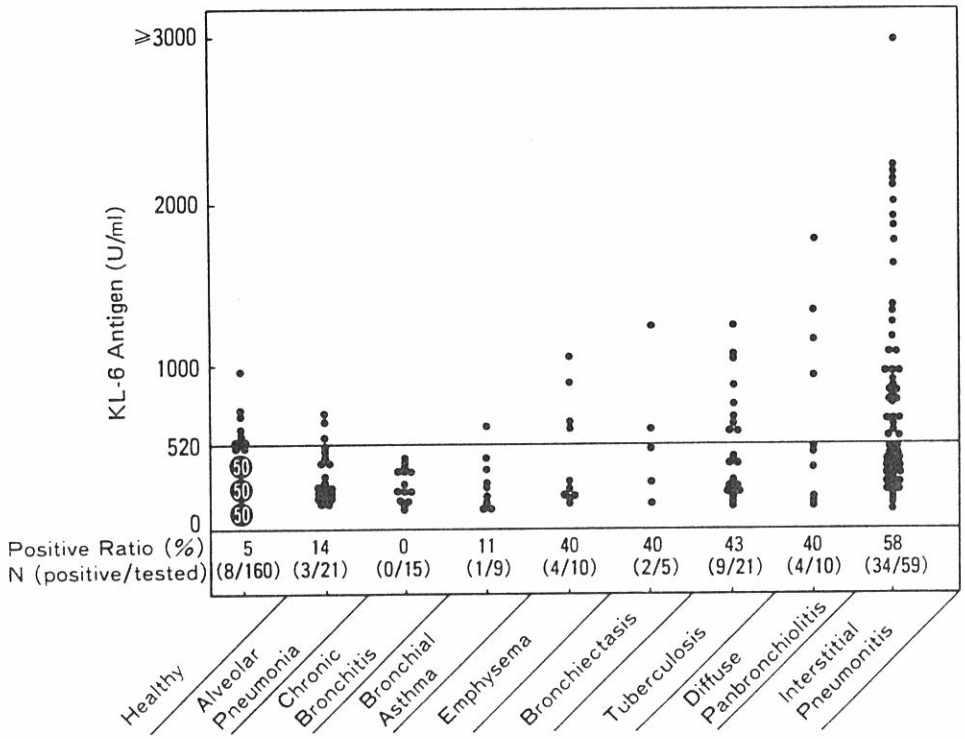

Figure 2. Levels of KL-6 antigen in sera from healthy controls and patients with nonmalignant lung diseases

図2．健常対照者と非悪性肺疾患患者の血清中のKL-6抗原値

tuberculosis, 40% (4/10) for diffuse panbronchiolitis, and 58% (34/59) for interstitial pneumonitis.

Figure 3 shows the levels of KL-6 antigen in the sera of interstitial pneumonitis patients classified by their etiology. The positive rates were 70% (19/27) for IIP, 100% (3/3) for hypersensitivity pneumonitis, 50% (5/10) for interstitial pneumonitis as a complication of collagen diseases, 60% (3/5) for radiation pneumonitis, 43% (3/7) for sarcoidosis, and 14% (1/7) for pneumoconiosis.

No significant correlation was observed between the levels of KL-6 antigen and LDH activity in the sera of 28 cases of interstitial pneumonitis, as shown in Figure 4. The proportion of serum samples with elevated LDH activity was only 11% (3/28), but that with elevated KL-6 antigen was 61% (17/28).

肺結核43％（9／21），瀰慢性汎細気管支炎40％（4／10），間質性肺炎58％（34/59）であった．

図3は病因別に分類した間質性肺炎患者における血清KL-6抗原値を示す．陽性率は各々，IIP 70％（19/27），過敏性肺炎100％（3／3），膠原病の合併症としての間質性肺炎50％（5／10），放射線誘発肺炎60％（3／5），サルコイドージス症43％（3／7），塵肺症14％（1／7）であった．

図4に示されているように，間質性肺炎28症例の血清中のKL-6抗原値とLDH活性との間に有意な相関はなかった．LDH活性が高値の血清検体の割合は11％（3／28）にすぎなかったが，KL-6抗原高値の検体は61％（17／28）であった．

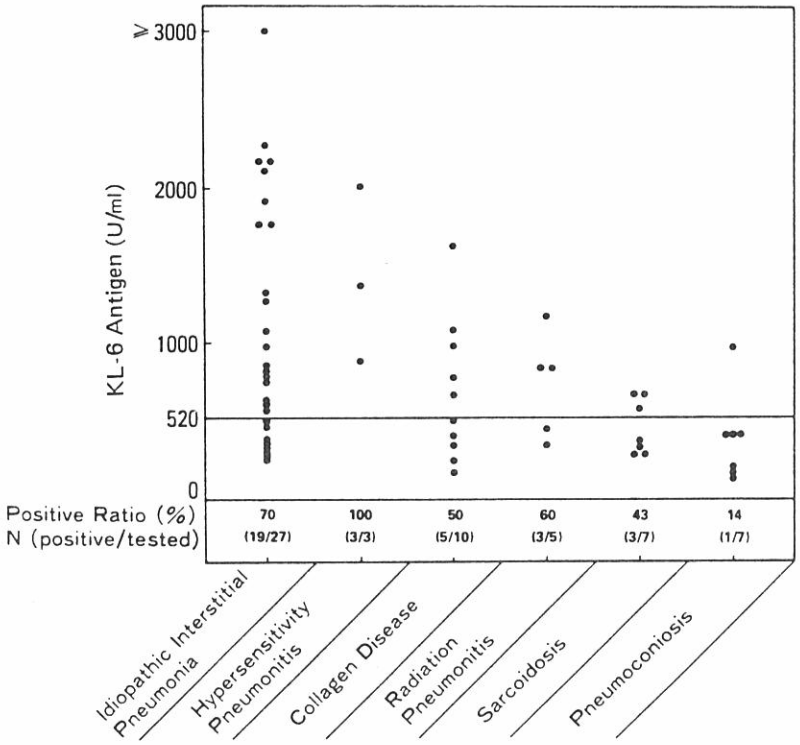

Figure 3. Levels of KL-6 antigen in sera from patients with interstitial pneumonitis

図3．間質性肺炎患者の血清中のKL-6抗原値

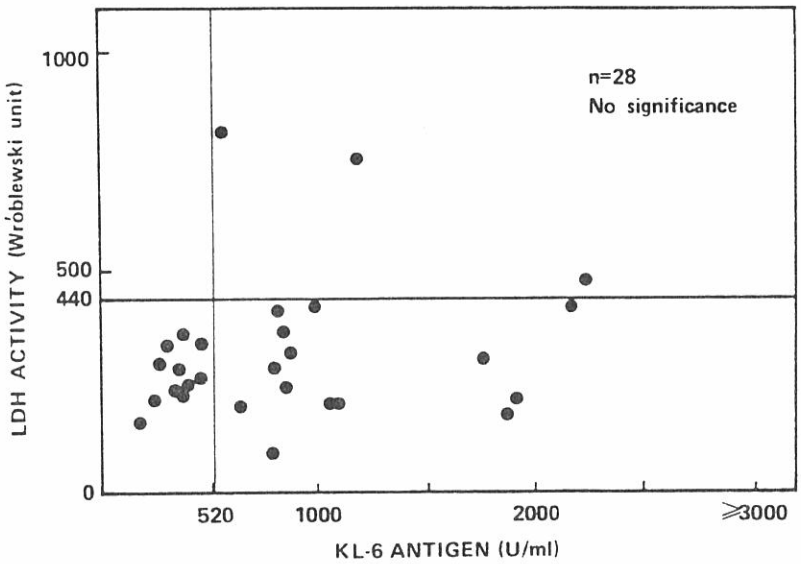

Figure 4. Serum levels of KL-6 antigen were compared with levels of serum LDH activity in interstitial penumonitis patients

図4．間質性肺炎患者の血清中のKL-6抗原値とLDH活性との比較

A ^{67}Ga-citrate scintigram was examined in 15 of the 27 IIP cases, whose KL-6 antigen levels were measured. Figure 5 shows that the positive rate of KL-6 antigen in the serum of 10 cases showing radioisotope uptake in their lung fields was 90% (9/10), while 5 cases, or 0% (0/5), showed no radioisotope uptake.

KL-6抗原値を測定したIIP 27症例のうち，15例について^{67}Ga-クエン酸シンチグラムを行った．図5に示すように肺への放射性同位元素の取り込みを示した10例の血清KL-6抗原の陽性率は90%（9/10）であったが，放射性同位元素の取り込みを示さなかった5例では陽性率は0%（0/5）であった．

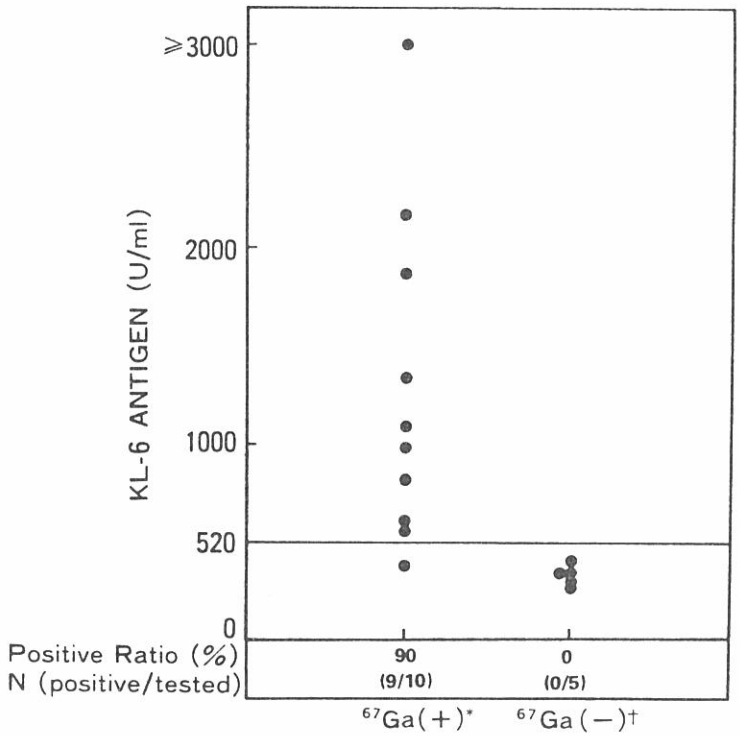

Figure 5. Levels of KL-6 antigen in sera from patients with idiopathic interstitial pneumonitis were compared between cases of positive ^{67}Ga-citrate uptake (*) and those of negative uptake (†)

図5．特発性間質性肺炎患者の^{67}Ga-クエン酸取り込み陽性症例（*）と陰性症例（†）との血清KL-6抗原値の比較

Figure 6 shows changes in serum KL-6 antigen levels for the 15 cases of interstitial pneumonitis who were examined twice during a one-month period. The changes in degree of clinical activity were evaluated from their subjective symptoms and objective signs including chest radiograph, pulmonary function tests, and arterial blood gas analysis. These cases were divided into three groups; improved, unchanged, and exacerbated. In the four improved cases, three cases of IIP and one case of pneumonitis complicated with rheumatoid arthritis, all the levels of KL-6 antigen decreased from abnormally high levels above 1,000 U/ml to

図6は1か月間に2回検査を受けた間質性肺炎15例の血清KL-6抗原値の変化を示す．臨床的活動性の程度の変化は自覚症状や胸部X線撮影写真，肺機能検査，動脈血ガス検査等から得られた客観的徴候により評価した．これらの症例を好転，不変，悪化という三つのグループに分けた．病状の好転した4例はIIP 3例と慢性関節リウマチ1人に併発した肺炎の1例であり，4例ともKL-6抗原値は1,000 U/ml以上の異常高値から低値へと減少した．

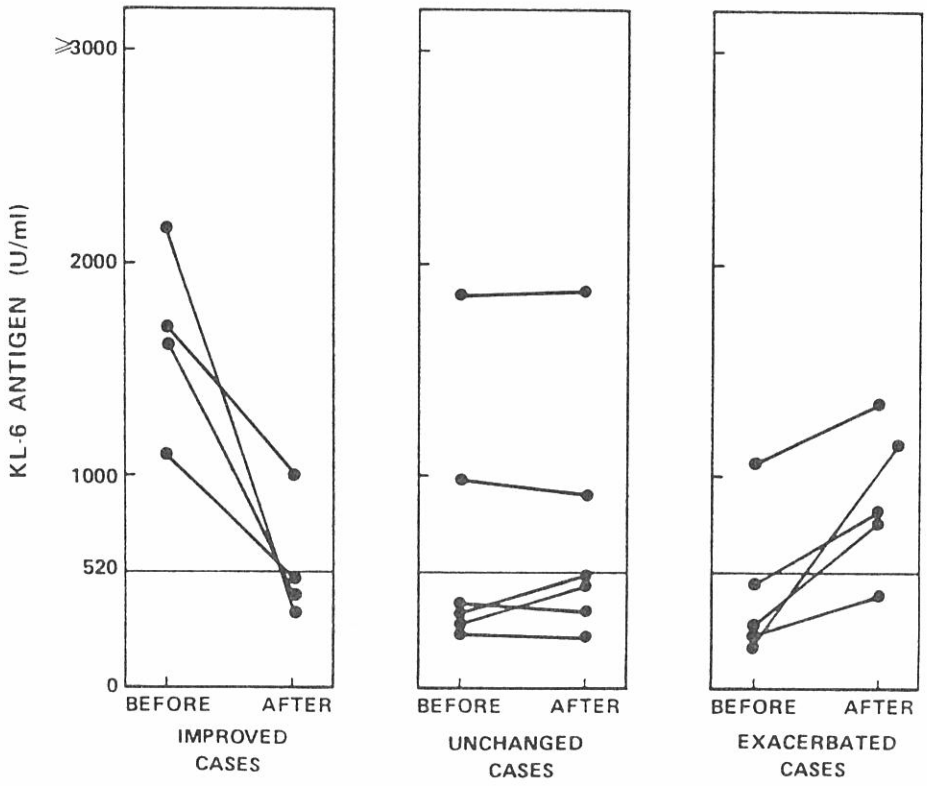

Figure 6. Changes of KL-6 antigen level in sera from patients with interstitial pneumonitis were examined over a period of one month and compared with their clinical outcome. In four improved cases, levels of KL-6 antigen decreased from abnormally high levels of over 1,000 U/ml. In six unchanged cases, the levels of serum KL-6 antigen changed only slightly. In five exacerbated lung cancer cases whose pneumonitis was caused by radiation therapy, the levels of serum KL-6 antigen increased after develoment of pneumonitis.

図6．間質性肺炎患者の血清KL-6抗原値の1か月間の変化を調べ，各々の臨床結果と比較した．軽快した4例ではKL-6抗原値は1,000 U/ml以上という異常な高値から低下した．病状の変化しなかった6例では血清KL-6抗原値はわずかしか変化しなかった．病状の悪化した5例は肺癌症例で，肺炎は放射線治療によるものであり，血清KL-6抗原値は肺炎発症後上昇した．

lower levels. Six cases in the unchanged group were diagnosed as IIP and their KL-6 antigen levels changed only slightly. The five cases in the exacerbated group were lung cancer patients whose pneumonitis were caused by radiation therapy. In three of the five cases, serum KL-6 antigen levels were within the normal range before irradiation but became abnormally high after pneumonitis developed. In another of these exacerbated cases, the serum KL-6 antigen level was abnormally high before irradiation and increased after pneumonitis

病状が不変のグループの6例はIIPと診断され，KL-6抗原値はほとんど変化しなかった．悪化したグループの5例は肺癌患者で，その肺炎は放射線治療によるものであった．5例中3例においては，血清KL-6抗原値は放射線治療前は正常範囲内であったが，肺炎発病後異常に高くなった．これら悪化した症例のうち別の1例では，血清KL-6抗原値が放射線治療前に異常に高く，肺炎発病後更に

developed. In the fifth case, the KL-6 antigen level was within the normal range throughout the period of observation, but did increase somewhat after developing pneumonitis following irradiation.

DISCUSSION

We have shown in this report that serum KL-6 antigen may be a useful marker for estimating the degree of clinical activity of interstitial pneumonitis. It was observed that the positive rate of elevated serum KL-6 antigen is very high in cases of interstitial pneumonitis, especially in those of IIP showing a positive uptake of ^{67}Ga-citrate in their lung field, and serum KL-6 antigen was clearly much more sensitive than serum LDH activity among interstitial pneumonitis patients. Furthermore, there was a significant positive correlation between the changes in serum KL-6 antigen levels and the subjective and objective signs of interstitial pneumonitis activity in patients whose clinical courses were followed.

This and previous[14] studies showed that non-malignant lung diseases showing high positive rates of elevated serum KL-6 antigen included not only interstitial pneumonitis but also emphysema, bronchiectasis, pulmonary tuberculosis, and diffuse panbronchiolitis. Extensive damage to the peripheral lung tissue appears to be a common histological change in these diseases. Since KL-6 antigens are expressed in high density on type II pneumocytes and cells of the respiratory bronchiolar epithelia, elevated serum KL-6 antigen levels might be caused by the release of KL-6 antigens from these two kinds of cells during degeneration and destruction of lung tissues and from type II pneumocytes during regeneration.

Examination of the serum KL-6 antigen level, combined with that of type III procollagen N-terminal peptides, may be clinically more useful, because the former, originating from type II pneumocytes and bronchiolar epithelial cells, reflects the tissue damage of parenchymal cells in the peripheral lung and the latter, metabolized from type III procollagen secreted by fibroblasts, reflects the proliferation of interstitial cells. Moreover, since the damage of parenchymal cells histologically precedes the fibrotic change of the interstitium in interstitial pneumonitis, KL-6 antigen may be elevated in an earlier phase than type III procollagen N-terminal peptides.

上昇した．残りの1例においては，KL-6抗原値は観察期間中ずっと正常範囲内であったが，放射線治療後肺炎を発病してから若干上昇した．

考　察

間質性肺炎の臨床的活動性の程度を推定する上で，有用なマーカーであると考えられる血清KL-6抗原について今回報告した．血清KL-6抗原増加の陽性率が，間質性肺炎の症例，特に肺への^{67}Ga-クエン酸の取り込みが陽性であったIIPの症例では非常に高いこと，また，間質性肺炎患者において血清KL-6抗原が血清LDH活性より顕著に高い感度を示すことが認められた．更に，臨床経過観察が行われた患者の血清KL-6値の変化と，間質性肺炎活動性の自覚症状や客観的徴候の変化との間には有意な正の相関があった．

今回と前回の研究[14]で血清KL-6抗原増加の高い陽性率を示す非悪性肺疾患には，間質性肺炎だけでなく，肺気腫，気管支拡張症，肺結核，瀰慢性汎細気管支炎が含まれることが示された．肺末梢組織への広範囲にわたる損傷が，これらの疾患に共通の組織学的病変であるようである．II型肺胞細胞や呼吸細気管支上皮細胞にKL-6抗原が高濃度に存在するので，血清KL-6抗原の増加は肺組織の変性，損傷中に両細胞や再生中にII型肺胞細胞からKL-6が放出されることにより起こるのかもしれない．

血清KL-6抗原値検査は，III型前膠原質N末端ペプチド値検査と併用すれば，臨床的により有用なものとなるであろう．なぜならば，前者はII型肺胞細胞や細気管支上皮細胞から生じるので肺末梢部の実質細胞の組織損傷を反映し，後者は線維芽細胞により分泌されたIII型前膠原質からの代謝生成物であるので，間質細胞の増殖を反映するからである．更に，間質性肺炎においては，実質細胞の損傷が間質の線維性変化より組織学的に先行するので，KL-6抗原はIII型前膠原質N末端ペプチドより早い段階で増加すると考えられる．

However, it is still not clear how sensitive the serum level of KL-6 antigen is in reflecting changes in lung tissue. It is difficult to clarify this relationship because repeated lung biopsies over a short time is practically impossible. Therefore, we will attempt to clarify the usefulness of serum KL-6 antigen as an indicator of the degree of clinical activity of interstitial pneumonitis by serial measurements in more cases, especially cases of radiation pneumonitis, the onset of which can be easily predicted.

しかし，血清KL-6抗原値が肺組織の病変に対してどれだけ感度が高いのかはまだ明確ではない．短期間に肺の生検を頻回に行うことは実際不可能であるので，両者の関係を明確にすることは困難である．したがって，間質性肺炎の臨床的活動性の程度の指標としての血清KL-6抗原の有用性を明確にするために，より多くの症例を，特にその発症時期が容易に予想できる放射線誘発肺炎の症例の値を，連続して測定するつもりである．

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