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Early detection of colon cancer by increased serum level of Krebs von den Lungen-6 in a patient with dermatomyositis-associated interstitial pneumonia

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Abstract. Krebs von den Lungen-6 (KL-6) is a high-molecular weight glycoprotein which is elevated in serum of patients with interstitial pneumonia (IP). Serum KL-6 level is clinically used for the diagnosis of IP as well as the evaluation of its disease activity. On the other hand, KL-6, which was originally identified when exploring novel soluble antigens in patients with lung cancer, is known to be elevated in patients with several malignant tumors. Here, we present the first patient in whom increased serum KL-6 led to the diagnosis of colon cancer during follow-up of dermatomyositis-associated IP. Because the risk of malignant tumors is high in IP patients with polymyositis and dermatomyositis, early detection of malignant tumors has a significant impact on their prognosis. The present case suggests that serum KL-6 is a possible tumor marker for early detection of malignant tumors in IP patients with polymyositis and dermatomyositis. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 265-270)*

Key words: KL-6, Interstitial pneumonia, Dermatomyositis, Tumor marker, Colon cancer

Introduction

Krebs von den Lungen-6 (KL-6) is a useful biomarker for diagnosing interstitial pneumonia (IP) and evaluating the disease activity of IP, such as idiopathic pulmonary fibrosis (IPF) and connective tissue disease-associated IP (1, 2). In fact, in addition to clinical symptoms, vital capacity, and the findings of chest roentography, serum KL-6 levels have been used to assess clinical improvement or worsening in patients with IP.

Elevated serum levels of KL-6 had been first demonstrated to be specific in patients with interstitial lung diseases including IP. However, further reports showed that serum KL-6 levels are increased in other respiratory diseases such as pulmonary alveolar proteinosis and lung cancer (particularly in lung adenocarcinoma) as well. KL-6 was originally found in lung adenocarcinoma, discovered when Kohno et al. tried to identify the novel tumor-associated antigens in sera and effusions, and it has been shown that serum KL-6 levels are sometimes elevated in patients with lung adenocarcinoma (3).

In patients with polymyositis and dermatomyositis (PM/DM), the prevalence of malignant tumors is known to be very high, and malignant tumors are often found during the follow-up of

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PM/DM patients. On the other hand, early detection of malignant tumors is sometimes difficult when patients do not show the relevant clinical symptoms.

We herein present a DM-associated IP patient in whom elevated serum KL-6 level led to the early detection and radical resection of colon cancer.

Case Presentation

A 67-year-old man who had been diagnosed with DM at the age of 47 was admitted to our hospital for evaluation of worsening exertional dyspnea that he had first noticed seven months previously. At the age of 47, he had presented with femoral muscle pain and was diagnosed as having DM with IP. Oral corticosteroid (prednisone 60 mg/day) and cyclophosphamide (100 mg/day) were given, and his symptoms gradually improved. Afterwards, cyclophosphamide was stopped, and the oral corticosteroid dose was tapered to 5 mg/day of prednisone. Three years following the corticosteroid reduction, he had no significant clinical symptoms, and serum creatinine kinase level was normal. Worsening of IP was not detected by annual follow-up with thoracic computed tomography (CT), and serum KL-6 levels remained around 800–1,000 U/ml. At the age of 66, serum KL-6 level suddenly increased to 5,000–7,000 U/ml, and he complained of adynamia of the lower extremities as well as exertional dyspnea. To assess the cause of his symptoms and the elevation of his serum KL-6 level, he was admitted to our hospital for further examination.

His clinical and occupational histories were not remarkable. He was a 27 pack-year former smoker and did not have a family history of IP, connective tissue diseases, or cancer. Physical findings on admission were as follows: height, 164 cm; body weight, 62 kg; body temperature, 36.9°C; blood pressure, 120/70 mmHg; pulse rate, 80 beats/minute; SpO2, 98% (under ambient air). His consciousness was clear. Fine crackles were present in both lung fields, and his abdomen was flat and soft with no tenderness. There was no edema or atrophy in the extremities.

The results of the laboratory examinations were as follows: serum lactate dehydrogenase, 235 IU/L; KL-6, 5,195 U/ml (reference < 500 U/ml); surfactant protein D, 197.9 ng/ml (reference < 110 ng/ml); surfactant protein A, 81.2 ng/ml (reference < 43.8 ng/ml). Autoimmune antibodies such as anti-Jo-1 antibody were all negative. Arterial blood gas analysis did not show hypoxia under ambient air, and a pulmonary function test revealed decreased lung diffusing capacity with normal vital capacity (Table 1). Chest roentgenograms showed reticular shadows in the bilateral lung fields (Figure 1A), and a chest CT revealed ground-glass opacities and curvilinear shadows in the bilateral dorsal lower lung fields (Figures 1B & C).

Because serum KL-6 levels were elevated, the disease activity of IP was suspected to have worsened. However, the findings of his CT as well as the serum levels of surfactant protein A and D, which are other biomarkers used for evaluating IP, did not show acute worsening of IP (Figure 2). Furthermore, no significant worsening of dermal or muscle symptoms without elevation of serum creatinine kinase and aldolase levels suggested that the disease activity of DM remained stable. To rule out other possible causes of serum KL-6 elevation, bronchoscopy was performed. Although the results of bronchoalveolar lavage showed an increase in total cell count (30.0 x 10^4/ml) and percentage of lym-

Table 1. Laboratory data on admission

Hematology					
WBC	9100	/μl	RF	1	IU/ml
Neu	81	%	ANA	<160	×
Lym	16	%	anti Jo-1 Ab	<0.5	U/ml
Mon	3	%			
RBC	4.28 x 10^6	/μl			
Hb	11.3	g/dl	KL-6	5195	U/ml
Ht	34	%	SP-A	81.2	ng/ml
Plt	32.2 x 10^4	/μl	SP-D	197.9	ng/ml
Biochemistry			Blood Gas Analysis (supine, room air)		
TP	7	g/dl	pH	7.41	
AST	24	IU/L	$PaCO_2$	39.6	Torr
ALT	17	IU/L	PaO_2	91.8	Torr
LDH	235	IU/L	HCO_3	24.6	mmol/l
ALP	247	IU/L	SaO_2	95.5	%
γGTP	21	IU/L	$AaDO_2$	8	Torr
T-bil	0.5	mg/dl			
BUN	12	mg/dl	Pulmonary Function Test		
Cr	0.87	mg/dl	VC	3.38	L
Na	140	mEq/L	%VC	102.4	%
K	4.2	mEq/L	FEV_1	2.55	L
Cl	107	mEq/L	FEV_1%	75.9	%
CK	117	IU/L	DLco	10.37	ml/min/mmHg
Aldolase	5.1	U/L	%DLco	42.6	%
			DLco/VA	2.67	ml/min/mmHg/L
Serology			%DLco/VA	60.4	%
CRP	0.06	mg/dl			
ESR	12	mm/hr			

RF: Rheumatoid factor, ANA: Anti-nuclear antigen, KL-6: Krebs von den Lungen-6, SP-A: Surfactant protein-A, SP-D: Surfactant protein-D

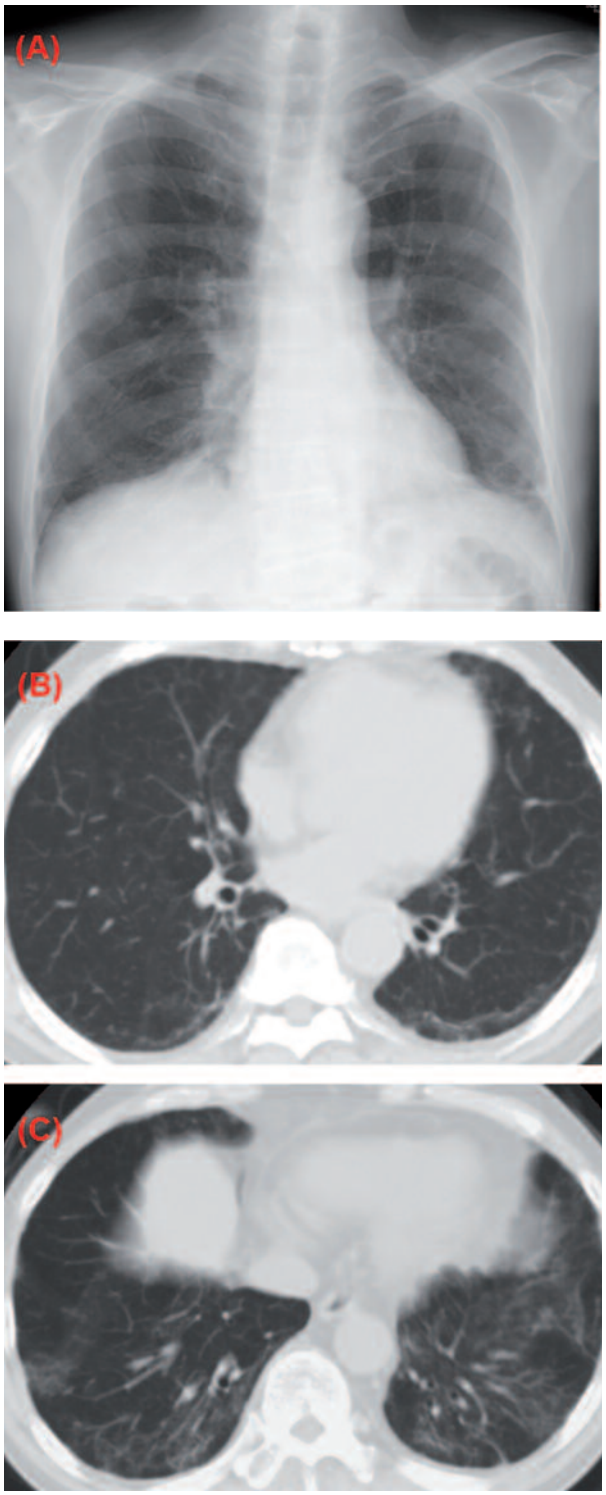

Fig. 1. Chest radiograph on admission (A) showed reticular shadows in the bilateral lung fields, and chest CT on admission (B, C) showed ground-glass opacities and curvilinear shadows in the bilateral dorsal lower lung fields.

phocytes (82.2%) in bronchoalveolar lavage fluid, and transbronchial biopsy suggested the presence of alveolitis, there were no findings suggestive of pulmonary alveolar proteinosis or lung cancer. At this point, acute worsening of IP and existence of other lung diseases were denied as the cause of serum KL-6 elevation. As KL-6 is known to be expressed in malignant tumors, we decided to perform an examination of the whole body for malignant tumors.

Because abdominal CT did not show the presence of malignant tumors, gastrointestinal endoscopy was performed. Esophagogastroduodenoscopy examinations revealed a 15-mm type IIc ulcerated lesion at the anterior wall of the pylorus of the stomach. The ulcerated lesion was proved to be adenocarcinoma by histological analysis. Colonoscopy was next performed, and a type 2 tumor was found in the ascending colon near the hepatic flexure. On histopathology, adenocarcinoma of the colon was diagnosed (Figure 3A). Right hemicolectomy was performed under the apprehension that the advanced colon carcinoma induced occlusive ileus. After resection of colon carcinoma, serum KL-6 level decreased to 2,462 U/ml. However, the level did not show a significant change after endoscopic submucosal dissection for type IIc gastric cancer.

As serum KL-6 level decreased after hemicolectomy, colon cancer was suspected to have caused elevation of serum KL-6 level. To verify this hypothesis, we performed immunohistochemical analysis using a colon cancer specimen. Colon cancer (Figures 3B & C), not normal colon tissues, resected from this patient clearly expressed KL-6. On the other hand, colon cancer resected from another patient with normal serum KL-6 level showed positive staining only in the apical membrane (Figure 3D).

Discussion

KL-6 is a high-molecular weight glycoprotein and has been widely used for the diagnosis of IP and the evaluation of its disease activity (1, 2, 4-6). Serum KL-6 level is reported to be elevated in IP such as IPF and connective tissue disease-associated IP. Follow-up of serum KL-6 levels is useful to evaluate disease activity, and increased serum KL-6 level suggests disease worsening in patients with IP. In the present case, serum KL-6 level was elevated dur-

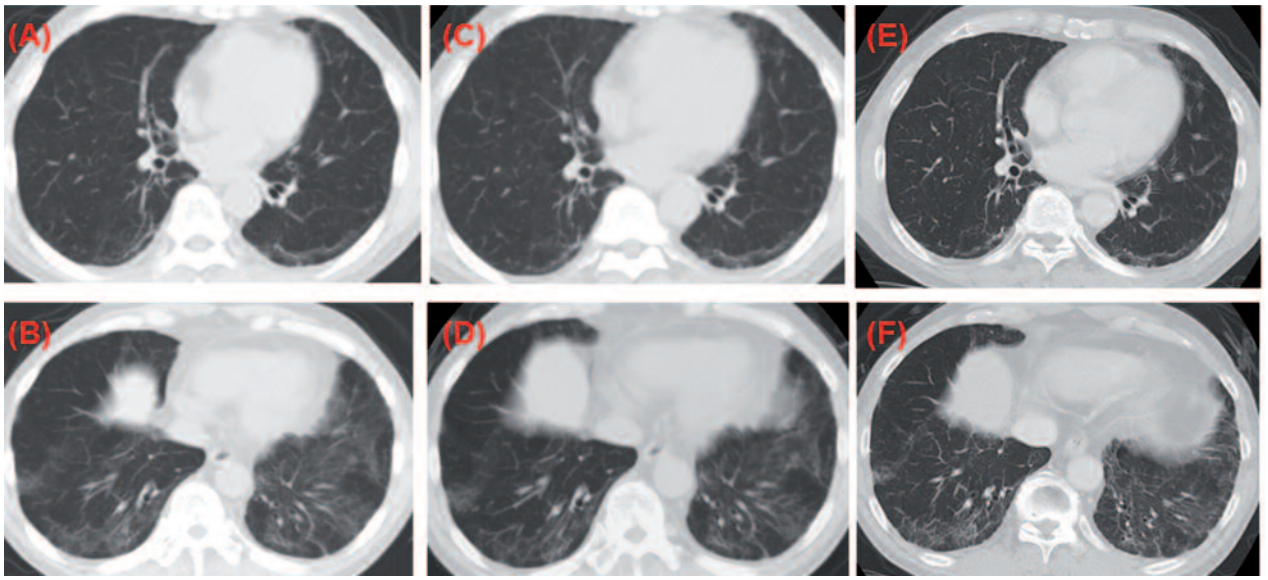

Fig. 2. The findings of follow-up chest CT showed that the extent of ground-glass opacity on CT taken 15 months before admission (A, B) and 7 months after resection of colon cancer (E, F) was not significantly changed compared to CT taken on admission (C, D)

ing follow-up of DM associated with IP; however, acute worsening of IP was not observed. Because KL-6 was originally found when the novel tumor-associated antigens were explored in lung adenocarcinoma, we performed an examination of the whole body to find possibly existing malignant tumor(s) in this patient. Adenocarcinoma was found in the colon and stomach, and, after resection of colon carcinoma, serum KL-6 level significantly decreased. In addition, immunohistochemical analysis showed the expression of KL-6 in the resected colon cancer.

In patients with PM/DM, increased risk of cancer has been reported. Hill et al. demonstrated that 198 out of 618 DM patients had cancer, 115 of whom developed cancer after they had been diagnosed with DM (7). Furthermore, among the 198 cancer patients, ovarian carcinoma was most frequent, followed by lung, pancreatic, stomach, and colorectal cancers. In this regard, physicians have to follow-up patients with PM/DM carefully to detect cancer development as early as possible. Other than lung cancer, several types of cancers, such as hepatocellular carcinoma, breast cancer, and cholangiocarcinoma, have been reported to express KL-6 (8-12). In fact, Kubo et al. showed that serum KL-6 was elevated in five out of seven PM/DM patients with malignant tumors (13), and others have reported similar results (14-16). Kiyoi et al. compared serum KL-6 levels before and after resection of colon cancer in two patients without IP and found that serum KL-6 levels which had been elevated before resection significantly decreased after resection in both patients (17). In addition, immunohistochemical analysis using the colon cancer tissues from these patients showed positive expression of KL-6.

Although these previous reports suggest the possibility of using serum KL-6 as a tumor marker in PM/DM patients with IP, at present there are only three reports available in English (two reports are written in Japanese and only their abstracts are available in English) (14-16). Two out of the three reports were on PM/DM-associated IP patients with ovarian cancer (15, 16), and the other was with pancreatic cancer (14). In all three patients, serum KL-6 levels were significantly elevated during follow-up in spite of no worsening of IP. In addition, serum KL-6 levels decreased after resection or chemotherapy in the ovarian cancer patients. However, no report yet exists comparing serum KL-6 levels in DM patients with IP before and after resection of colon cancer.

In the present case, immunohistochemical analysis showed that KL-6 was expressed in the cytoplasm of colon cancer cells. According to the im-

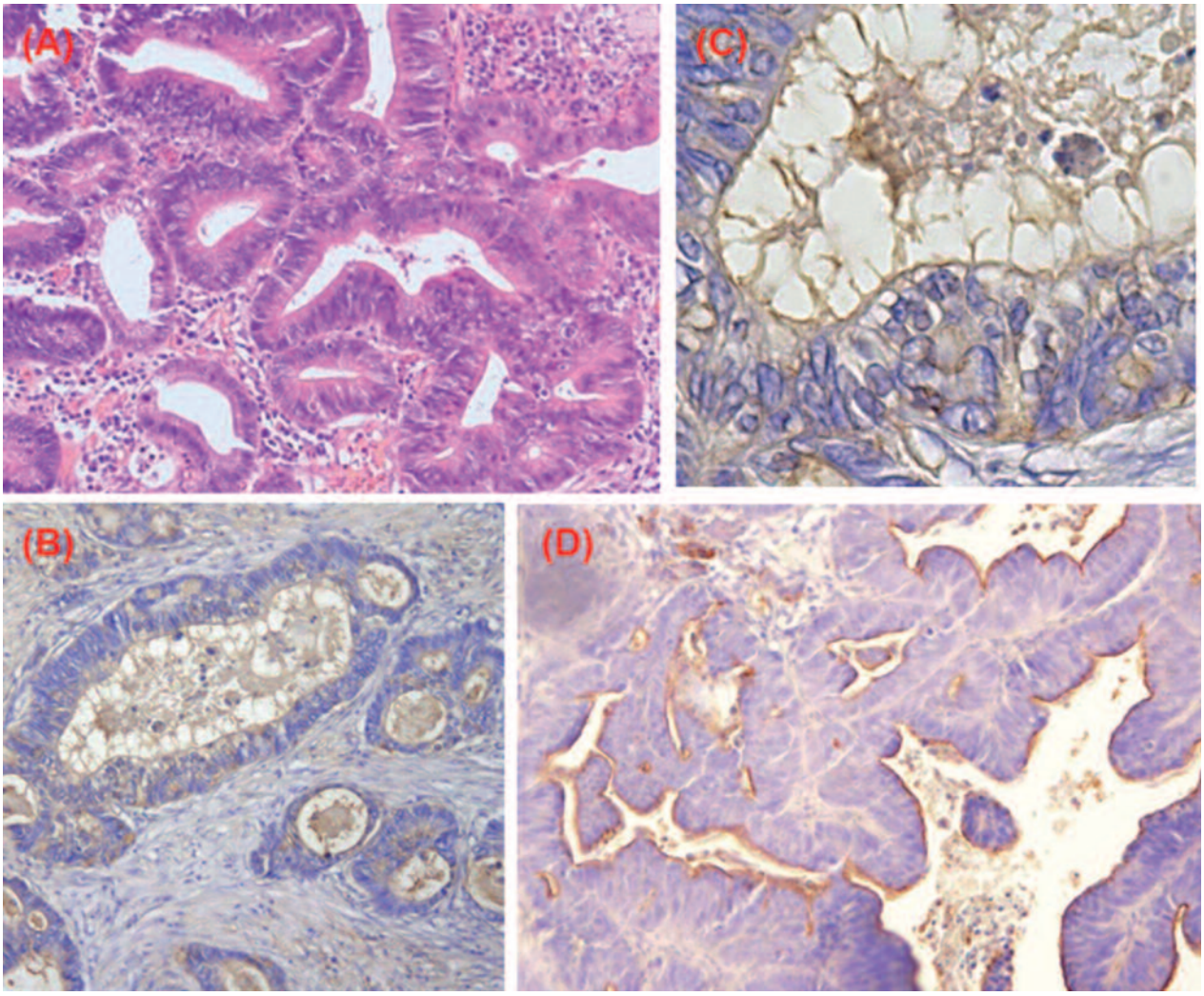

Fig. 3. Colonoscopy revealed a type 2 tumor in the ascending colon near the hepatic flexure. The pathological findings of the biopsy specimen showed adenocarcinoma (A; hematoxylin and eosin stain). Immunohistochemical analysis for KL-6 revealed clear staining in the cytoplasm of colon cancer tissues from the present case (B, C). On the other hand, colon cancer resected from another patient with normal serum KL-6 level showed positive staining only in the apical membrane (D). Magnification: x 100 (A, B, D), x 400 (C)

munohistochemical analysis of 82 colorectal adenocarcinoma patients by Guo et al., 29 showed positive staining only in the apical membrane and 47 showed positive staining in the circumferential membrane and/or cytoplasm (18). Interestingly, the five-year survival rate of the patients showing positive staining in the circumferential membrane and/or cytoplasm (63.0%) was significantly worse compared to that of the patients showing positive staining only in the apical membrane (85.7%) and those showing no staining (100%). Although the mechanism(s) of different KL-6 staining patterns in these patients is not clear, the results suggest the possibility that the prognosis of these patients might be predicted by analyzing the staining pattern of KL-6. Although the relationship between the staining pattern of KL-6 and serum KL-6 level has not yet been clarified, in our case, serum KL-6 level was elevated in the patient with positive staining in the cytoplasm and did not in another patient with positive staining only in the apical membrane. These results suggest the possibility of a relationship between staining patterns and serum KL-6 levels in colon cancer patients.

To the best of our knowledge, this is the first

case report comparing serum KL-6 level in a DM patient with IP before and after resection of colon cancer. Our patient had gastric cancer, and the level of serum KL-6 was not sufficiently decreased to the average range before this patient complicated with colon cancer. Although the exact reason(s) of insufficient decrease of serum KL-6 cannot be identified, we believe colon cancer is, at least in part, involved in an increase of serum KL-6 in the present case because the serum KL-6 level significantly decreased after colon cancer resection and immunohistochemical analysis showed KL-6 expression in colon cancer. Because the early-stage gastric cancer cannot increase serum KL-6, slight worsening of IP before admission and/or after operation for colon cancer may increase the level of serum KL-6. In any case, it was fortunate that colon cancer was curatively resected in the present case. Colon cancer at a relatively early stage may not be detected by follow-up images such as CT. In IP patients with DM/PM, gastrointestinal endoscopic examinations should be considered when serum KL-6 level is significantly elevated despite no worsening of IP. Although the clinical usefulness of serum KL-6 has been reported especially from Japanese groups, the 2010 official ATS/ERS/JRS/ALAT statement of IPF focused upon KL-6 as a serum biomarker (19), and serum KL-6 has recently been demonstrated to be increased in German patients with interstitial lung diseases as well as Japanese (20). In this regard, it is becoming important to know the unusual cases with increased serum KL-6 to take care of patients with IP.

Here, we reported the first patient in whom increased serum level of KL-6 led to the early detection of colon cancer during follow-up of DM-associated IP. The present case suggests that serum KL-6 is a possible tumor marker for early detection of malignant tumors in IP patients with DM/PM.

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References

1. Totani Y, Demura Y, Ameshima S, Ishizaki T, Miyamori I. The usefulness of serum KL-6 levels for the diagnosis of disease activity in idiopathic interstitial pneumonia]. Nihon Kokyuki Gakkai Zasshi 2000; 38(6): 437-441.
2. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. Respir Investig 2012;50(1):3-13.
3. Kohno N, Akiyama M, Kyoizumi S, Hakoda M, Kobuke K, Yamakido M. Detection of soluble tumor-associated antigens in sera and effusions using novel monoclonal antibodies, KL-3 and KL-6, against lung adenocarcinoma. Jpn J Clin Oncol 1988;18(3):203-216.
4. Kohno N, Awaya Y, Oyama T, et al. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis 1933;148(3):637-642.
5. Kobayashi J, Kitamura S. KL-6: a serum marker for interstitial pneumonia. Chest 1995;108(2):311-315.
6. Kambe M, Ohshimo S, Kohno N. Immunity tests for respiratory diseases-SP-A, SP-D, KL-6. Rinsho Byori 2007;55(4):381-387.
7. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet 2001;357(9250):96-100.
8. Gad A, Tanaka E, Matsumoto A, et al. Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma. World J Gastroenterol 2005;11(42):6607-6612.
9. Ogawa Y, Ishikawa T, Ikeda K, et al. Evaluation of serum KL-6, a mucin-like glycoprotein, as a tumor marker for breast cancer. Clin Cancer Res 2000;6(10):4069-4072.
10. Xu H, Inagaki Y, Tang W, et al. Elevation of serum KL-6 mucin levels in patients with cholangiocarcinoma. Hepatogastroenterology 2008;55(88):2000-2004.
11. Kawata T, Tsukagoshi H, Mashimo T, et al. KL-6-producing invasive thymoma. Intern Med 2002; 41(11):979-982.
12. Ohtsuki Y, Kuroda N, Umeoka T, et al. KL-6 is another useful marker in assessing a micropapillary pattern in carcinomas of the breast and urinary bladder, but not the colon. Med Mol Morphol 2009; 42(2):123-127.
13. Kubo M, Ihn H, Yamane K, et al. Serum KL-6 in adult patients with polymyositis and dermatomyositis. Rheumatology (Oxford) 2000; 39 (6):632-636.
14. Kida Y, Maeshima E, Furukawa K, Ichikawa T, Goda M, Ichinose M. A case of polymyositis with a significantly high level of KL-6 associated with pancreatic cancer. Mod Rheumatol 2007;17(3):262-264.
15. Kodera M, Usuda T. A case of dermatomyositis with significantly high level of KL-6 associated with ovarian cancer. Ryumachi 2002; 42(2):694-698.
16. Uchida A, Sugihara M, Ito S, et al. Ovarian cancer with swelling of the right upper arm, amyopathic dermatomyositis, and elevated serum KL-6. Nihon Naika Gakkai Zasshi 2006;95(4):742-744.
17. Kiyoi M, Yoshimasu T, Ota F, Naito K, Hirai Y, Okamura Y. [Two cases of rectal cancer metastasizing to the lung with a high serum KL-6 level. Nihon Geka Gakkai Zasshi 2008;22(6):79-84.
18. Guo Q, Tang W, Inagaki Y, et al. Clinical significance of subcellular localization of KL-6 mucin in primary colorectal adenocarcinoma and metastatic tissues. World J Gastroenterol 2006;12(1):54-59.
19. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788-824.
20. Horimasu Y, Hattori N, Ishikawa N, et al. Different MUC1 gene polymorphisms in German and Japanese ethnicities affect serum KL-6 levels. Respir Med012;106(12):1756-64.