Int J Clin Exp Pathol 2017;10(3):3310-3314
www.ijcep.com /ISSN:1936-2625/IJCEP0045527

Original Article

Clinical value of serum KL-6 for lung diseases in patients with polymyositis and dermatomyositis

Yumeng Liu, Yumiao Zhao, Aiguo Xu

Critical Section, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

Received December 1, 2016; Accepted January 7, 2017; Epub March 1, 2017; Published March 15, 2017

Abstract: Objective: To investigate clinical value of serum KL-6 for lung diseases in patients with polymyositis and dermatomyositis. Methods: 77 cases of PM/DM patients, among them 27 cases with interstitial lung disease (ILD), 20 cases with infectious lung disease, 30 cases without lung disease. ELISA method was adopted to measure the KL-6 levels of serum. The association with KL-6 and diagnosis, clinical features, laboratory indexes, treatment, even and prognosis were analyzed. Results: The average values of the KL-6 levels of serum in PM/DM patients with ILD, PM/DM patients with infectious lung disease, and PM/DM patients without lung diseases were (1135.33 ± 648.67), (371.85 ± 187.14), (231.00 ± 110.89), respectively. PM/DM patients with ILD had significantly higher median KL-6 levels of serum compared with other two groups, and the difference is statistically significant ($P < 0.05$), but the difference between PM/DM patients with infectious lung disease and PM/DM patients without lung disease had no statistical significance ($P = 0.229$); While the 507 U/ml was regarded as positive standard, the sensitivity of KL-6 for PM/DM interstitial lung disease diagnosis was 96.3%, and the specificity was 89.0%; Serum levels of KL-6 were inversely correlated with DLco%, VC%, and TLV% (all $P < 0.05$). In serum KL-6 increased group, anti-Jo-1 positive rate was higher than normal group ($P < 0.05$). A follow-up analysis indicated that, KL-6 levels of serum of 10 cases of PM/DM with ILD patients were associated with therapeutic effect ($P < 0.05$), and KL-6 levels of serum of 5 cases died of PM/DM with ILD patients were significantly higher than those of 22 cases of PM/DM with ILD patients surviving ($P < 0.05$). Conclusion: KL-6 levels of serum can be used to identify interstitial lung disease and infectious lung disease, and assess clinical response to treatment, and a high level of KL-6 possibly indicates a poor prognosis.

Keywords: Polymyositis, dermatomyositis, KL-6, interstitial lung disease

Introduction

KL-6 is a high molecular weight glycoprotein found in the 1980s [1]. It is mainly secreted by type II epithelial cells of alveoli. Previously regarded as a tumor marker of thymoma and many studies are done on interstitial lung disease recently [2], it has a strong chemotaxis towards fibroblasts and plays an important role in fibrosis in the process of disease [3]. Polymyositis (PM) and dermatomyositis (DM) are a group of systemic autoimmune diseases characterized by inflammation of striated muscle. It is mainly accumulated in skin, gastrointestinal tract, heart, lung and other organs. Interstitial lung disease (ILD) is the most common pulmonary complication with high incidence rate and it is an important factor affecting the prognosis of PM/DM patients [4]. Early diagnosis of ILD and early treatment are the key to stopping the disease changing from ground-glass attenuation into irreversible honeycomb shape. At present, there is no clinically specific serum marker to determine the incidence of ILD, treatment outcome and prognosis. Therefore, this study aims to evaluate the clinical significance of KL-6 in the complication ILD developing from PM/DM through detecting its level.

Objects and methods

Research object

A total of 77 patients with PM/DM who were admitted to our hospital from May, 2015 to May, 2016 were chosen as the research object, including 22 males and 55 females, with age ranging from 17 to 80 years old and an average age of (52 ± 15) years old. Their average dis-

Table 1. Mean value of serum KL-6 of each group

Group	Number of patients	KL-6 (U/ml)
PM/DM combined with ILD	27	1135.33 ± 648.67
PM/DM combined with pulmonary infection	20	371.85 ± 187.14
PM/DM without lung disease	30	231.00 ± 110.89

ease course ranges from 1 month to 108 months with a mean value of (17 ± 27) months. There are 27 patients combined with ILD 27, 22 patients combined with pulmonary infection and 30 patients without lung disease. There was no statistical significance in the differences between different age groups and gender groups. PM/DM is consistent with the IIM diagnostic criteria proposed by Bohan/Peter in 1975. ILD was diagnosed and confirmed through pulmonary function test, chest radiograph (X ray or ARCT) or lung biopsy. The symptom of some patients was consistent with clinical feature of pulmonary infection which was confirmed by etiological examination. Chest HRCT or X-ray examination was conducted to exclude patients with interstitial lung disease. Exclusion criteria: ① interstitial pneumonia combined with pulmonary infection; ② combined with other autoimmune diseases; ③ combined with malignant tumors.

Research method

The patients who were diagnosed with PM/DM received fasting hemospasia and were divided into four groups according to the diagnostic criteria. After collection, blood samples were centrifuged with 1000 g centrifugal force at 4°C and serum was collected 10 minutes after the centrifugation and preserved for test at -80°C. KL-6 concentration was measured by double-antibody sandwich ELISA and the porous Eitest KL-6 kit produced by the Shanghai Maisha Corporation were used to obtain the mean value.

Statistical analysis

The measurement data was analyzed by SPSS 17.0 and indicated by $\bar{x}$ ± s. W normality test was adopted to analyze the differences of mean value between two different groups, t test was adopted to analyze the normal distribution and Mann-Whitney U test was adopted to analyze the abnormal distribution; LSD-t test was adopted to analyze the comparison of two samples from different groups, chi-square test was adopted to analyze the enumeration data, ROC curve was adopted to analyze the cut-off value, sensitivity and specificity of diagnosis, and spearman's rank correlation was adopted to analyze the correlation; now that $P < 0.05$, it is believed that there is statistical significance in differences.

Results

Concentration of serum KL-6 in ILD group, pulmonary infection group and the group without lung disease

The mean of KL-6 concentration in each group is shown in **Table 1**. According to the LSD-t test, it was found that the serum KL-6 level in the ILD group was significantly higher than that in the other two groups and there was statistical significance in the differences ($P < 0.05$); but there is no statistical significance in the differences between pulmonary infection group and the group without lung disease ($P = 0.229$). The ROC curve analysis showed that the positive cutoff value of PM/DM patients combined with interstitial lung disease was 507 U/ml, the sensitivity was 96.3%, and the specificity was 89.0%. The ROC curve of KL-6 in the serum of patients with PMD/DM combined with interstitial lung disease is shown in **Figure 1**.

Correlation between KL-6 levels of serum and clinical feature of patients with PM/DM and laboratory indexes

Further study was conducted on the correlation between KL-6 levels of serum and clinical feature and laboratory indexes for patients with PM/DM. According to Spearman rank correlation analysis, there was significant negative correlation among the KL-6 levels, the proportion of carbon monoxide diffusion capacity to predicted value (DLco%) ($r = -0.765$, $P < 0.01$), the proportion of vital capacity to predicted value (VC%) ($r = -0.584$, $P < 0.01$) and the proportion of total lung capacity to predicted value (TLC%) ($r = -0.635$, $P < 0.01$). However, there is no significant correlation among the KL-6 lev-

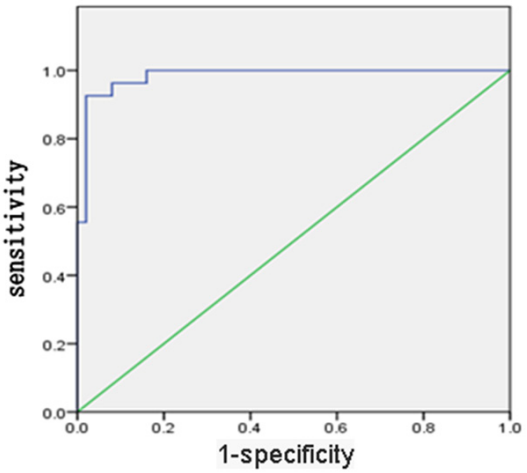

Figure 1. ROC curve of serum KL-6 in PM/DM combined with interstitial lung disease.

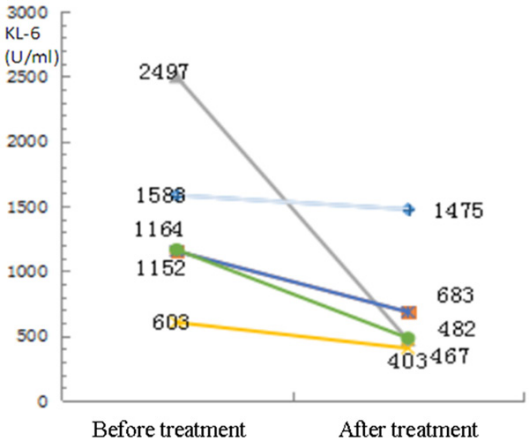

Figure 2. Trend of Serum KL-6 before and after treatment (improved group).

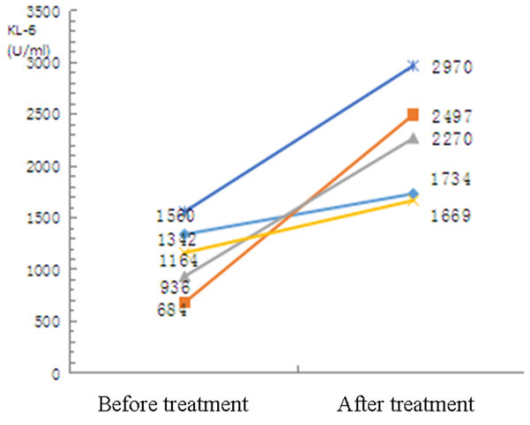

Figure 3. The Trend of Serum KL-6 before and after Treatment (deteriorated group).

els, the proportion of forced expiratory volume in one second to the predicted value (FEV1%), the proportion of forced vital capacity to the predicted value (FVC%), FEV1/FVC, the proportion of residual volume to the predicted value (RV%), ferritin, C-reactive protein, erythrocyte sedimentation rate (ESR), creatine kinase (CK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), CD3, CD4, CD8 and CD4/CD8 ($P > 0.05$). In addition, the positive rate of anti-JO-1 antibody in the group with higher serum KL-6 level was higher than that in the normal group (= 4.472, $P = 0.034$). There is no statistical significance in the differences in anti-JO-1 antibody, other positive antibodies, such as ANA, SSA, SSB, Sm, RNP, RF, etc., and clinical feature, such as cough, dyspnea, dysphagia, myasthenia, arthritis/arthralgia, rash, Reynolds phenomenon etc. between the group with higher serum KL-6 level and the normal group.

Correlation between serum KL-6 and therapeutic effect

The treatment situations of 10 patients with PM/DM combined with ILD was followed up and the comparison of serum KL-6 before and after treatment was tested with Wilcoxon test. It showed that the difference between before and after treatment was statistically significant ($P < 0.05$). The serum KL-6 concentration in the improved group was also lower than that in the deteriorated group, as shown in **Figures 2** and **3**.

Effect of serum KL-6 level on prognosis

Through follow-up visits of the PM/DM patients combined with ILD for 1-13 months, it was found that 5 patients died and the serum KL-6 level in the dead patients (mean: 2663.60 ± 348.49) was significantly higher than that in the surviving patients (mean: 995.14 ± 459.18). There was no statistical significance in the difference between the two groups ($t = 7.596$, $P < 0.05$).

Discussion

Patients with PM/DM combined with ILD was diagnosed and confirmed mainly based on pulmonary function test, chest radiograph (X or ARCT) or lung biopsy. However, some critically ill patients could not complete pulmonary func-

tion test, repeated radiograph examination will bring a negative impact on the physical health and lung biopsy is invasive operation without clinically convenient and effective specificity index. In addition, patients with PM/DM combined with ILD and pulmonary infection are clinically common, but the two diseases have completely different treatment protocols and are not easy to identify and distinguished; wrong diagnosis will seriously affect prognosis. Therefore, correct early diagnosis of patients with PM/DM combined with ILD is an urgent clinical problem to solve. The results of this study showed that KL-6 was a useful serum index to successfully diagnose PM/DM combined with ILD and distinguish ILD from pulmonary infection. The sensitivity and specificity of KL-6 diagnosis were respectively 96.3% and 89.0%. According to the results, the sensitivity of the diagnosis was high, but specificity was relatively low. Maybe KL-6 expression of other interstitial lung disease could also be high [5], such as idiopathic interstitial pneumonia, allergic pneumonia, radioaction pneumonia, drug-induced pneumonia and pulmonary alveolar proteinosis, etc. In addition, some existing studies showed that serum KL-6 level was also high in the other connective tissue diseases accompanied with ILD, such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, mixed connective tissue diseases [6-8]. The concentration of serum KL-6 in PM/DM combined with ILD group was significantly higher than that in the group with pulmonary infection and group without lung disease; the serum KL-6 concentration in the PM/DM combined with ILD was about 3 times of that in the pulmonary infection group and 5 times of that in the group without lung disease, there was statistical significance in the differences. However, there was no significant difference between the pulmonary infection group and the group without lung disease. Therefore, it showed that KL-6 could be used as a serum index to distinguish PMD/DM with ILD and PMD/DM with pulmonary infection.

ILD lung function changes are mainly manifested by limited dysfunction and/or diffusion dysfunction. This study showed that KL-6 level was negatively correlated with DLco%, VC% and TLC% and it suggested that KL-6 could directly reflect the degree of alveolar damage in patients. Anti-Jo-1 antibody is one of the aminoacyl-tRNA synthetases. According to the study of Taggart [9], the positive rate of anti-JO-1 antibody in PM/DM patients combined with ILD can be as high as 50%-75%. This study showed the positive rate of anti-JO-1 antibody in the group with higher serum KL-6 level is higher than that in the normal group, directly suggesting that KL-6 is correlated with ILD.

It was found through follow-up visits of 10 PM/DM patients combined with ILD that there was an obvious decrease in the serum KL-6 level in the improved group, while there was an obvious increase in the serum KL-6 level in the deteriorated group. There was statistical significance in the difference between before treatment and after treatment and it suggested that regular testing of KL-6 level could effectively reflect treatment effect and facilitate clinical treatment. The studies of Fathi [10] also showed that KL-6 levels of serum can reflect the extent of alveolar damage, and can prompt the outcome of treatment. In addition, it was found through follow-up visits of PM/DM patients combined with ILD for 1-13 months that the serum KL-6 level of 5 dead patients was significantly higher than that of 22 survived patients and about 3 times of that of the survived patients. Therefore, high serum KL-6 level might indicate bad outcome of treatment.

In summary, serum KL-6 can be used as a serum index to indicate whether PM/DM patents have ILD, the outcome of treatment and prognosis and to guide clinical diagnosis and treatment.

Acknowledgements

Science and Technology Department of Henan Province (No. 16B310008); Medical science and technology project of Henan Province (No. 201503061).

Disclosure of conflict of interest

None.

Address correspondence to: Yumiao Zhao, Critical Section, The First Affiliated Hospital of Zhengzhou University, 2001 Jianshe Road, Zhengzhou 450052, Henan Province, China. Tel: +86-13503837625; E-mail: yumiaozzu@126.com

References

[1] Kohno N, Awaya Y, Oyama T, Yamakido M, Akiyama M, Inoue Y, Yokoyama A, Hamada H, Fujioka S, Hiwada K. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients witn interstitial lung disease. Am Rev Respir Dis 1993; 148: 637-642.

[2] Vij R, Noth I. Peripheral blood biomarkers in idiopathic pulmonary fibrosis. Transl Res 2012; 159: 218-227.

[3] Xu L, Yan DR, Zhu SL, Gu J, Bian W, Rong ZH, Shen C. KL-6 regulated the expression of HGF, collagen and myofibroblast differentiation. Eur Rev Med Pharmacol Sci 2013; 17: 3073-3077.

[4] Meyer KC, Raghu G, Baughman RP, Brown KK, Costabel U, du Bois RM, Drent M, Haslam PL, Kim DS, Nagai S, Rottoli P, Saltini C, Selman M, Strange C, Wood B; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American thoracic society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 2012; 185: 1004-1014.

[5] Ohshimo S, Ishikawa N, Horimasu Y, Hattori N, Hirohashi N, Tanigawa K, Kohno N, Bonella F, Guzman J, Costabel U. Baseline KL-6 predicts increased risk for acute exacerbation of idiopathic pulmonary fibrosis. Respir Med 2014; 108: 1031-1039.

[6] Oguz EO, Kucuksahin O, Turgay M, Yildizgoren MT, Ates A, Demir N, Kumbasar OO, Kinikli G, Duzgun N. Association of KL-6 levels of serum with interstitial lung disease in patients with connective tissue disease: a cross-sectional study. Clin Rheumatol 2016; 35: 663-666.

[7] Hua-Huy T, Riviere S, Tiev KP, Dinh-Xuan AT. Use of pulmonary function tests and biomarkers studies to diagnose and follow-up interstitial lung disease in systemic sclerosis. Rev Pneumol Clin 2014; 70: 335-342.

[8] Takahashi K, Nakamura H, Takenouchi K, Iizawa N, Koiwa M, Sato A, Mochizuki Y, Watanabe H, Takai S. Serum KL-6 elevation and possible pulmonary involvement in patients with rheumatoid arthritis treated with biological agents. J Nippon Med Sch 2014; 81: 364-371.

[9] Taggart AL, Finch MB, Courtney PA, Gormley GJ. Anti-jo-1 myositis: “mechanic’s hands” and interstitial lung disease. Ulster Med J 2002; 71: 68-71.

[10] Fathi M, Barbasso Helmers S, Lundberg IE. KL-6: a serological biomarker for interstitial lung disease in patients with polymyositis and dermatomyositis. J Intern Med 2012; 271: 589-597.