

# Rheumatoid Arthritis with High Serum KL-6 Complicating Malignant Tumor: Two Case Reports

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## Abstract

Interstitial pneumonia develops not only as a rheumatoid arthritis (RA) manifestation, but also due to the side effects of drugs for its treatment, leading to the necessity of regular examinations. Krebs von den Lungen-6 (KL-6) is often used to check the activity of interstitial pneumonia in RA patients. However, this marker is also produced by some malignant tumors, and a high level of serum KL-6 has been reported in cancer patients. We describe herein 2 cases of RA with the complication of a malignant tumor not involving the lung, although there is no lesion in the lung regardless of the high level of serum KL-6.

## Keywords

KL-6, Malignant Tumor, Rheumatoid Arthritis, SP-D

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## 1. Introduction

Rheumatoid arthritis (RA) causes chronic and progressive synovitis of several joints, and finally destroys various joints. Among the extra-articular manifestations of RA, lung or blood vessel lesions markedly influence the prognosis. Interstitial pneumonia develops not only as an RA manifestation, but also due to the side effects of drugs for its treatment, leading to the necessity of regular examinations. Krebs von den Lungen-6 (KL-6) is one

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of the proteins expressed on alveolar epithelial and bronchial epithelial cells, and this marker is often used to check the activity of interstitial pneumonia. However, this marker is also produced by some malignant tumors, and a high level of serum KL-6 has been reported in cancer patients [1]-[3].

We describe herein 2 cases of RA with the complication of a malignant tumor not involving the lung, although there is no lesion in the lung regardless of the high level of serum KL-6. The patients and their families were informed that data from their cases would be submitted for publication, and they provided their consent.

## 2. Case Presentation

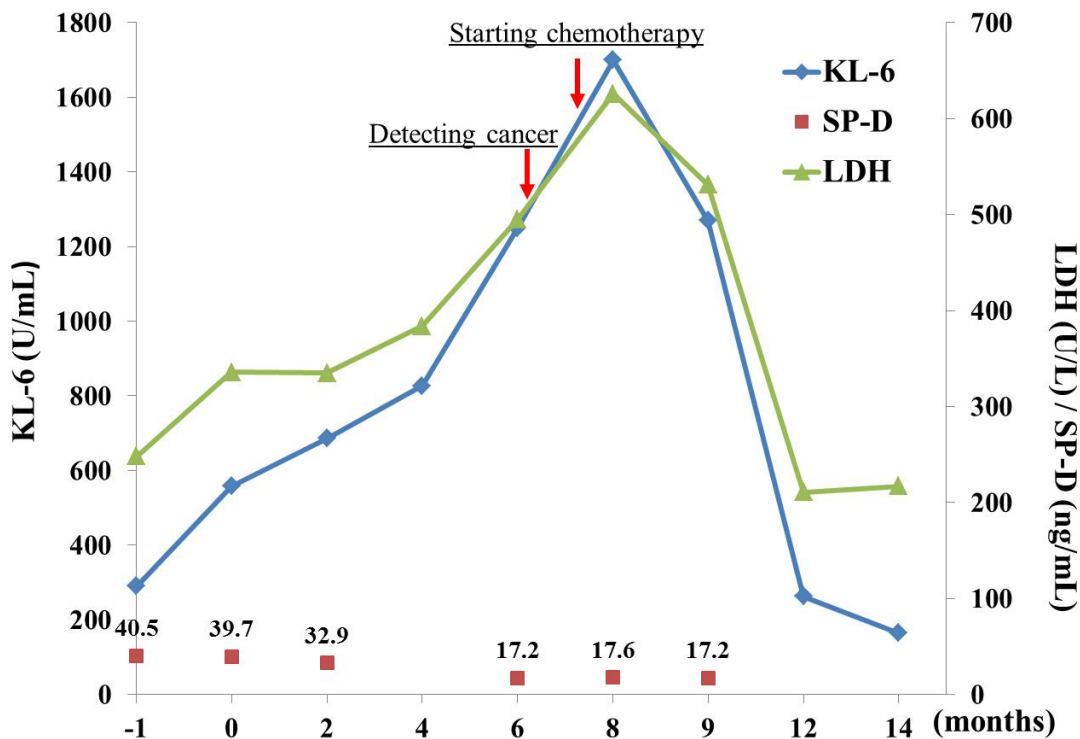
### Case 1 (Figure 1)

A 54-year-old woman had been treated for RA in our hospital for 16 years, and she took methotrexate (MTX) (6 mg/week), salazosulfapyridine (SASP) (1000 mg/day), and prednisolone (PSL) (4 mg/day), and received the injection of infliximab (IFX), a total of 1800 mg, for 8 months. Although there were no symptoms involving respiratory organs, serum KL-6 (549 U/mL, normal range < 500 U/mL) and lactate dehydrogenase (LDH) (336 U/L, normal range 115 - 245 U/L) were high on regular laboratory examinations. However, serum surfactant protein-D (SP-D) was in the normal range (39.7 ng/mL, normal range < 110 ng/mL). Even though we examined her in detail by computed tomography (CT) suspecting interstitial pneumonia, there was no lung abnormality. So, we continued to treat her with IFX.

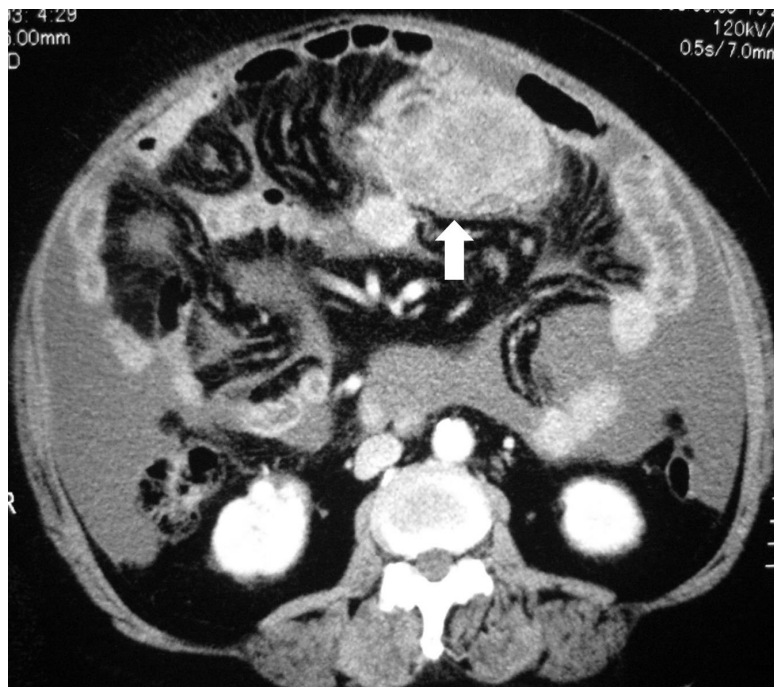
Because KL-6 gradually became elevated and too high (1250 U/mL) 5 months after KL-6 elevation, we re-examined her by CT. Ascites was shown at the edge of the liver, and ovarian cancer was identified on detailed examination involving abdominal echo, CT, and magnetic resonance imaging (MRI) (Figure 2). She could not undergo surgical treatment because of peritoneal dissemination, and was treated with chemotherapy. Her cancer reduced and KL-6 entered the normal range (263 U/mL) 5 months after chemotherapy. However, her condition worsened again, and she died 1 year and 10 months after starting chemotherapy.

### Case 2 (Figure 3)

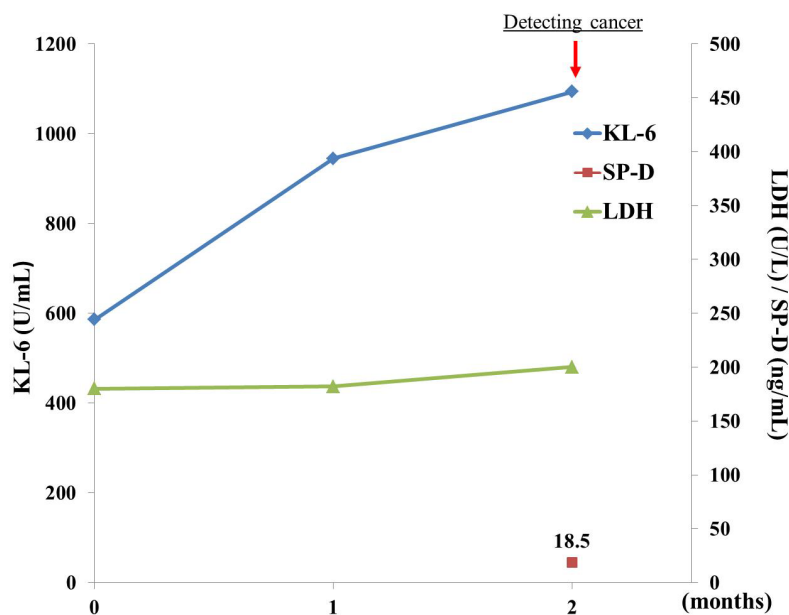
A 73-year-old woman had been treated for RA by SASP in our hospital for 2 months. Even though serum KL-6 was high (586 U/mL) on laboratory tests at the first medical examination, there was no abnormality on lung radiography. Although KL-6 (1094 U/mL) was gradually elevated, SP-D (18.5 ng/mL) and LDH (200 U/L) were



**Figure 1.** Clinical course of KL-6, SP-D, and LDH in case 1. Although KL-6 and LDH were gradually increased, SP-D was in the normal range. KL-6 and LDH were decreased after chemotherapy.



**Figure 2.** Abdominal axial image of computed tomography (CT). CT showed a large intraabdominal tumor (white arrow).



**Figure 3.** Clinical course of KL-6, SP-D, and LDH in case 2. Although KL-6 was gradually increased, SP-D and LDH were in their normal ranges.

in their normal ranges. We examined her whole body suspecting cancer, and colon cancer with peritoneal dissemination was identified by CT, MRI, and colonoscopy. She could not undergo surgical treatment or chemotherapy. She died 2 months after being diagnosed with the tumor.

### 3. Discussion

Lung lesions are the most frequent and important of RA lesions excluding those of joints. Furthermore, intersti-

tial pneumonia is the most frequent among RA lung lesions. In addition, drug-induced interstitial lung disease is also an important complication in RA treatment. Serum levels of KL-6, SP-D, and LDH are useful for the early detection of lung lesions, and we should examine these parameters regularly to observe the transition in RA patients. KL-6 is a high-molecular-weight glycoprotein identified by Kohno and belonging to Mucin-1 (MUC1), and it is useful for detecting and observing interstitial pneumonia [4]. SP-D is mainly expressed on alveolar type II cells, and it is present at a high level in the serum in the presence of interstitial pneumonia in the active phase [5]. LDH is an enzyme showing a high level in the serum on cell injury, and it also shows a high serum level in interstitial pneumonia. Lung lesions related to RA show high levels of these parameters, like idiopathic interstitial pneumonia. Because we can start to treat lung lesions early after confirming their existence based on imaging examination, these parameters are important.

Initially, KL-6 was identified as a tissue and serum marker of lung adenocarcinoma, so this marker often shows a high level in the serum in the presence of adenocarcinomas, such as lung adenocarcinoma, pancreatic carcinoma, and breast cancer [1]-[3]. Therefore, it is possible to use it as a nonspecific tumor marker. There have been some reports that serum KL-6 was increased in ovarian cancer patients, and Matsunaga *et al.* reported that the positive rate of KL-6 was high in 154 ovarian cancer patients, and 88% of progressive ovarian cancer patients were positive [6]. Regarding the digestive organs, there have been some reports on colon cancer, and some stated that KL-6 may play an important role in the metastasis of colon cancer [7]-[9]. Although we consider that the cause of KL-6 elevation is from MUC1 expression in various tumor cells, detailed causes have not been elucidated [10]. Therefore, we should be aware of the complication of a malignant tumor when we examine RA patients who show high KL-6 and normal SP-D or LDH on serum examinations, as in our cases.

Regarding RA-related diseases, there have been some reports of the complication of a malignant tumor with KL-6 elevation in dermatomyositis patients [11]. However, to date, there have been no reports of the complication of a malignant tumor with KL-6 elevation in RA patients. Although serum KL-6 showed a high level in the present cases, SP-D was in the normal range. In consideration of the fact that CT did not show interstitial pneumonia and KL-6 was normalized by chemotherapy, KL-6 may have arisen from tumor cells in the present cases.

#### 4. Conclusion

In conclusion, the present cases demonstrate the complication of a malignant tumor although there is no lesion in the lung regardless of the high level of serum KL-6. We should search for malignant tumors in RA patients with high KL-6 and without high SP-D and LDH, showing interstitial pneumonia on CT.

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