Serum KL-6 level as a monitoring marker in a patient with pulmonary alveolar proteinosis

Masamitsu Nakajima, Toshiaki Manabe, Yoshihito Niki, Toshiharu Matsushima

Abstract
A raised serum level of KL-6 is known to exist in active pulmonary fibrosis and KL-6 may be produced and secreted by type II pneumocytes. A case is described of pulmonary alveolar proteinosis with high serum KL-6 levels. The serum KL-6 level decreased after whole lung washing and correlated with symptoms, opacities on the chest radiograph, and arterial blood gas measurements. The serum KL-6 level may represent a useful marker for pulmonary alveolar proteinosis.

Keywords: KL-6; pulmonary alveolar proteinosis; tumour marker

KL-6 is a mucin-like high molecular weight glycoprotein which is now classified as cluster 9 (MUC-1). The serum level of KL-6 is known to be an indicator of disease activity in pulmonary fibrosis. We have previously reported that KL-6 is produced and secreted in the serum by pulmonary type II pneumocytes. Pulmonary alveolar proteinosis is characterised by deposition of proteinaceous material in air spaces. This material consists of lipid bilayer membranes separated by amorphous proteinaceous material containing phospholipids and proteins similar to surfactant or one of its components. The cause of this condition remains unclear, but it is probably related to either overstimulation of type II pneumocytes and/or an impairment in the mechanisms for removal of alveolar phospholipids. We describe a patient with pulmonary alveolar proteinosis who had high serum KL-6 levels which were monitored before and after whole lung washings.

Case report
A 40 year old man who presented with exertional dyspnoea was found to have non-segmental bilateral reticular infiltration shadows in the middle and lower lung fields on the chest radiograph (fig 1A). A chest CT scan revealed diffuse ground glass opacity with thickening of the interlobular septum and a peripheral clear zone (fig 1B). In October 1991 a diagnosis of pulmonary alveolar proteinosis was confirmed by the grossly milky opacity of the bronchoalveolar lavage (BAL) fluid, histopathological findings of a transbronchial lung biopsy specimen (fig 2A), a biochemical analysis of phospholipids, and an electron microscopic study of the lavage fluid. With the patient breathing room air, his arterial blood gas values were as follows: pH 7.45; Pao₂ 8.53 kPa. Other laboratory data revealed a haemoglobin level of 15.6 g/dl, a white blood cell count of 4500/µl with normal differentials, an erythrocyte sedimentation rate of 3 mm/h, and C reactive protein (CRP) of 0.3 mg/dl. Blood chemical analysis demonstrated a high serum lactate dehydrogenase (LDH) level of 198 IU/l. Analysis of bronchoalveolar lavage fluid revealed total cells of $24.5 \times 10^5$ cells/ml. The percentages of macrophages, lymphocytes and neutrophils from the recovered cells were 99%, 1% and 0%, respectively. Whole lung washing alleviated his symptoms, affected the shadows on his chest radiographs, and brought his blood gas values towards normal. However, in 1992, 1993, 1994, and 1996 he was admitted to hospital with dyspnoea and the ground glass opacities on the chest radiographs were con-
sistent with recurrence of pulmonary alveolar proteinosis. Total bilateral whole lung lavages were performed on two different occasions, about two weeks apart. We examined the KL-6 levels with a sandwich-type enzyme linked immunosorbent assay (EIA) using KL-6 monoclonal antibody (IgG1) in serum and whole lung washing fluids (fig 2B). The serum KL-6 levels were extremely high before whole lung washing, but decreased and were within the normal range after whole lung washing in December 1994 and February 1996. The level of KL-6 in whole lung washing fluid was 100 000 U/ml. The serum levels of KL-6 correlated with symptoms, opacities on the chest radiographs, and PaO₂ levels (fig 3). Immunostaining with monoclonal KL-6 antibody (mouse IgG) was performed on transbronchial lung biopsy specimens using the avidin-biotin-peroxidase complex (ABC) method. There was strongly positive immunoreactivity for KL-6 to the alveolar epithelium. This was confirmed using a positive control of pulmonary fibrosis with type II cell hyperplasia and negative controls of paraquat lung in which type II cells are completely lost as well as those of omission of primary antisera.

Discussion

Pulmonary alveolar proteinosis is a disease of unknown cause with accumulation of surfactant-like substance in alveolar and bronchiolar lumina. Pulmonary surfactant is a complex mixture of lipids and proteins which are produced and secreted by pulmonary type II pneumocytes. Interstitial fibrosis is not usually seen. BAL and whole lung washing are useful treatments for pulmonary alveolar proteinosis. Some patients with pulmonary alveolar proteinosis do not require more than one or two lavages or whole lung washings and few patients require them to be repeated semi-annually or annually.

KL-6 has been reported as a new serum marker for indicating the disease activity in patients with pulmonary fibrosis. We have previously reported that KL-6 is produced and secreted by pulmonary type II pneumocytes. However, the mechanism of the production of KL-6 from pulmonary type II pneumocytes is still unknown, and further studies are necessary.

We have reported that some glycoproteins and tumour markers such as carcinoembryonic antigen (CEA), sialyl LeX (SLX), and carbohydrate antigen 15–3 (CA 15–3) are found in high levels in whole lung washing fluid, and that they were produced by type II pneumocytes in a patient with pulmonary alveolar proteinosis. Serum KL-6 levels were extremely high before whole lung washing and correlated with dyspnoea, arterial blood gas analysis (PaO₂), and the degree of opacities on the chest radiographs before and after whole lung washing. In this case serum carcinoembryonic antigen (CEA) and CA 15–3 levels were also examined and were found to be slightly raised before washing and decreased afterwards. These findings suggest that type II cell pneumocytes could produce not only glycoproteins such as CEA and CA 15–3, but also a high molecular glycoprotein such as KL-6. As a result, the serum KL-6 level could be a useful indicator and monitoring marker for pulmonary alveolar proteinosis.

Variable indicating markers in pulmonary alveolar proteinosis including chest radiographic findings, serum LDH levels, and blood
Serum KL-6 levels have been reported. The level of PaO2, correlated with symptoms, but serum LDH levels did not and there was a high LDH level after the first whole lung washing in 1996. In this case, serial measurements of serum KL-6 and LDH levels revealed that KL-6 correlated more closely with disease activity than serum LDH levels.

Previous reports have shown that the serum KL-6 level is a useful marker for pulmonary fibrosis. However, in this case pulmonary fibrosis was not prominent because the chest radiographic findings, pulmonary function test results, and blood gas analysis results were almost normal after whole lung lavage. We have shown that the serum KL-6 level can be raised in pulmonary alveolar proteinosis without pulmonary fibrosis. Although pulmonary alveolar proteinosis is a rare disease, we should be aware that a high serum KL-6 level exists in the disease and that it could be an indicator and a good monitoring marker.


Reactivation of coccidioidomycosis in a fit American visitor

F M K Williams, V Markides, J Edgeworth, A J Williams

Abstract

The case history is presented of an American visitor, known to have had primary coccidioidomycosis previously, who became very unwell during a visit to the UK. Despite consideration of reactivation of coccidioidomycosis from the outset, other pathogens were identified while Coccidioides immitis was not initially, leading to a delay in treatment. (Thorax 1998;53:811–812)

Keywords: coccidioidomycosis; diagnosis

Coccidioidomycosis is a fungal infection endemic in the south western United States, Mexico, and Central and South America. Infection by the organism Coccidioides immitis usually produces a mild ‘flu-like illness or no symptoms at all,’ and previous exposure to C immitis may be detected by serological and skin testing.

Case report

A 48 year old Caucasian man had developed a ‘flu-like illness followed by dyspnoea and a productive cough shortly after arriving in the UK for a Christmas holiday. He had lived all his life in California and was working as a park ranger, but denied contact with animals. He was a life non-smoker and had no risk factors for human immunodeficiency virus (HIV). He presented to the referring hospital and was found to have signs of bilateral pneumonia. There was a neutrophil leucocytosis (total white cell count (WCC) 11.2 × 10⁹), arterial blood gases on air revealed hypoxaemia (pH 7.54, PaO2 6.8 kPa, PaCO₂ 2.9 kPa, SaO₂ 91%), and the chest radiograph showed consolidation in the left mid and lower zones and the right lower zone. Two years previously he had had “valley fever”, a self-limiting infection caused by C immitis which had manifested as a ‘flu-like illness and an abnormal chest radiograph. As is usual in valley fever, skin tests had become positive and the illness had resolved without treatment.

The patient had been admitted to the referring hospital and intravenous cefuroxime and erythromycin were administered. Culture of purulent sputum revealed a heavy growth of group A β haemolytic streptococcus (GABHS) and the influenza A titre was raised and fell three weeks later (1 in 128 to 1 in 40). The working diagnosis was severe streptococcal pneumonia secondary to influenza, and this was supported subsequently by raised streptolysin O (300) and DNAse titres (800) which subsequently fell to 100 and 300, respectively. The referring team considered reactivation of coccidioidomycosis but sputum sent to Bristol Public Health Laboratory Service failed to grow C immitis and serological tests were also negative. Despite this, and a negative HIV test, amphotericin B was started 10 days after admission because the patient failed to improve.
On the 15th day he was transferred. On arrival, oxygen saturation on air was 86%, WCC 17.6 (neutrophils 13.6, eosinophils 0.4 x 10^9/l), and C reactive protein 233 mg/l. The chest radiograph showed more extensive consolidation with extension to the right middle lobe (fig 1). Fibreoptic bronchoscopy was performed and two transbronchial biopsy and bronchoalveolar lavage (BAL) specimens were taken from the right lower lobe. Microscopic examination of the BAL fluid revealed a large number of white cells, predominantly neutrophils, but no organisms, and histological examination of the biopsy specimen showed chronic pneumonia without granulomas or spherules on silver stain. The patient continued to deteriorate. Six days later \textit{C immitis} was grown from both the BAL fluid and admission sputum samples. Repeat serological tests sent at the time of transfer returned strongly positive for \textit{C immitis} (1:640 by complement fixation). Amphotericin B (1 mg/kg) was recommenced. Over the next two weeks bilateral pleural effusions developed and microscopic examination of this bloodstained exudate showed occasional fungi but no growth on culture. Such high serological titres predict dissemination\(^1\) but cerebrospinal fluid examination was normal and a bone scan was negative. Over the subsequent three weeks his clinical condition improved and \textit{C immitis} complement fixation titre fell to 1:80. Amphotericin B was given until a total dose of 1 g was reached and oral fluconazole 400 mg a day was substituted. HIV serology remained negative.

**Discussion**

This case raises several interesting points. Firstly, the diagnosis of coccidioidomycosis was not easy to confirm despite being considered throughout and, secondly, none of the usual causes of reactivation were present.

A recent review of coccidioidomycosis states that difficulty in making the diagnosis usually arises from failure to consider the organism.\(^1\) In this case coccidioidomycosis was considered from the outset and evidence of other infections did not deter either team from an active search for \textit{C immitis}. He was documented to have had primary coccidioidomycosis two years previously which had resolved completely. Recurrent coccidioidomycosis arises by one of two mechanisms\(^4\): reactivation of the primary infection in individuals who become immunocompromised—for example, by HIV, malignancy, immunosuppressive drugs, diabetes and alcoholism—or by repeat exogenous infection in those exposed to high levels of the organism, typically laboratory workers handling the organism.\(^3\) None of these risk factors was identified.

We believe that the initial stages of pneumonia were caused by GABHS. Although it is possible that GABHS came from the pharynx, he did not complain of sore throat, the culture was a heavy pure growth and the ASO/DNase titres support infection. GABHS pneumonia is an unusual and severe bacterial pneumonia and influenza is known to predispose to it, especially in children.\(^5\) The patient also developed extensive pulmonary coccidioidomycosis. It is possible that he had ‘flu complicated by GABHS pneumonia and that, in the context of this severe pulmonary infection, reactivation of coccidioidomycosis occurred. This would explain why culture of \textit{C immitis} was negative initially. We know of no other case of bacterial infection per se leading to reactivation and surmise that GABHS pneumonia was sufficiently immunosuppressing to have caused reactivation coccidioidomycosis.

Serum KL-6 level as a monitoring marker in a patient with pulmonary alveolar proteinosis

Masamitsu Nakajima, Toshiaki Manabe, Yoshihito Niki and Toshiharu Matsushima

Thorax 1998 53: 809-811
doi: 10.1136/thx.53.9.809

Updated information and services can be found at:
http://thorax.bmj.com/content/53/9/809

These include:

References
This article cites 10 articles, 1 of which you can access for free at:
http://thorax.bmj.com/content/53/9/809#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Pulmonary alveolar proteinosis (12)
- Interstitial lung disease (559)
- Radiology (diagnostics) (812)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/