Review Article
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Serum krebs von den lungen-6 (KL-6): a promising biomarker in sarcoidosis

Abstract

Sarcoidosis is a multi-system inflammatory disease of unknown origin characterized by non-caseating epithelioid cell granuloma and lymphocytic alveolitis.1 It has unidentified etiology, heterogeneous clinical presentation and unpredictable disease course. Since injury and regeneration of type II pneumocytes is a significant histological feature of Sarcoidosis, substances derived from type II pneumocytes have been the focus of research in Sarcoidosis and other interstitial lung diseases. One important biomarker under research for Sarcoidosis is the high molecular weight glycoprotein, Krebs von den Lungen-6 (KL-6). KL-6 is a glycoprotein present on the membrane of type 2 alveolar cells, bronchiolar epithelial cells and also on epithelial cells of other organs.2 It is reported to be elevated in the serum and broncho-alveolar lavage (BAL) fluid of patients with Sarcoidosis. Its role in patients with Interstitial Lung Diseases (ILDs) and connective tissue diseases is being studied.3 It has been revealed that serum KL-6 is elevated in 70–100% of patients with parenchymal sarcoidosis and in 30-70% of patients with other forms of Sarcoidosis. In this review, we highlight the use of KL-6 as a biomarker in the diagnosis and severity of pulmonary sarcoidosis.

Keywords: Serum KL-6, biomarker, Sarcoidosis

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Introduction

Sarcoidosis is a multiorgan disorder of unknown etiology.[4] It affects young and middle aged adults. The most common presentations are bilateral hilar lymphadenopathy and pulmonary infiltration followed by ocular and skin involvement. Other organs that may be affected are liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles and bones. Clinic-radiological correlation with histological evidence of non-caseating epithelioid cell granulomas is essential to establish the diagnosis of sarcoidosis. However, granulomas of other causes and local sarcoid reactions must be excluded before establishing the diagnosis of sarcoidosis. In sarcoidosis, there is diminished cutaneous delayed-type hypersensitivity and increased helper T cell type 1 (Th1) immune response at the site of disease. Circulating immune complexes and B cell hyperactivity are also found. The course of disease and prognosis may correlate with the presentation on onset and the extent of the disease. For example, an acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually follows a self-limiting course while an insidious onset, especially with multiple extra-pulmonary lesions often leads to progressive fibrosis of the lungs and other organs. This review discusses the clinical application of KL-6 as one of the most promising serological biomarkers for patients Sarcoidosis. Literature was obtained from medical databases including PubMed and Web of Science.

Review

Diagnostic Approach

The diagnosis of Sarcoidosis cannot be established by presence of non-caseating granulomas in a single organ like skin. The diagnostic work-up for patients with sarcoidosis should provide the following details:

1. Histologic confirmation of the disease,
2. The extent and severity of organ involvement,
3. Assess whether the disease is stable or is likely to progress, and
4. Determine the effect of therapy on the patient.

High resolution computed tomography (HRCT), bronchoscopic examination and surgical lung biopsy (SLB) are the basic investigations required to make a definite diagnosis of sarcoidosis.[5–7] Transbronchial lung biopsy (TLB) is the procedure of choice in most cases. Its diagnostic yield depends largely on the experience of the operator, ranging from 40% to more than 90% when four to five lung biopsies are carried out.[8] Serial pulmonary function testing is used to monitor disease activity and predict the outcome in these patients.[9] These investigations for initial evaluation require specific medical facilities and may result in considerable discomfort to patients (Table 1). Hence, the identification of serum biomarkers would significantly improve the diagnostic methods. Serum biomarkers are easy to perform, reproducible and less invasive. Several serum biomarkers have been tested for their use in the various ILDs.[10–16] Among these, biomarkers derived from type II pneumocytes have been of particular interest, because ILDs show a common pathophysiological development, i.e., type II pneumocyte injury and remodelling.[10] The most widely used biomarkers for ILDs derived from type II pneumocytes are KL-6 and the surfactant proteins, SP-A and SP-D. These 3 biomarkers have been studied independently by two Japanese research groups (Hiroshima University and Sapporo Medical University) and are currently in wide clinical use in Japan. Lactate dehydrogenase (LDH) has also been used as a biomarker for ILDs in Japan; however, LDH serum level is not specific for lung damage and has been superseded by KL-6, SP-A and SP-D.[10] BUN - blood urea nitrogen; DLCO - diffusing capacity of the lung for CO; ECG - electrocardiogram.

Table 1 Recommended Initial Evaluation in patients with sarcoidosis.[3]

S. No	occupational and environmental exposure, symptoms
1	History (occupational and environmental exposure, symptoms)
2	Physical examination
3	Postero-anterior chest radiography
4	Pulmonary function tests: spirometry and DLCO
5	Peripheral blood counts: White blood cells, red blood cells, platelets
6	Serum chemistries: calcium, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase), creatinine, BUN
7	Urine analysis
8	ECG
9	Routine ophthalmologic examination
10	Tuberculin skin test

Krebs von den Lungen-6 (KL-6)

KL-6 is a mucin-like high molecular weight glycoprotein that is expressed on Type II pneumocytes and respiratory bronchiolar epithelial cells.[17,18] It is the soluble component in the pulmonary epithelial lining fluid produced by proteolytic cleavage. KL-6 is released into the blood vessel when these cells are proliferating, stimulated or injured, as the barrier is damaged. Thus, KL-6 is a marker of Alveolar epithelial cell injury. It has chemotactic and proliferative effects on fibroblasts and correlates with fibrogenesis. Serum levels of KL-6 are elevated in various respiratory and non-respiratory conditions, including breast and pancreatic cancers [19,20] and diabetes mellitus.[21] This observation has led to a focus on the use of KL-6 as a diagnostic and prognostic tool in respiratory diseases.

Serum and broncho-alveolar lavage fluid levels of KL-6, first described by Kohno et al.[22] in 1988, were raised in patients with interstitial pneumonia.[17,18,23] Several investigators have also reported that KL-6 is a useful serum marker to confirm diagnosis and for long-term management in patients with diffuse pulmonary diseases. Patients with idiopathic pulmonary fibrosis or non-specific interstitial pneumonia have also showed significant elevation in KL-6 levels.[24–29] Several studies show that the serum KL-6 level is elevated in patients with sarcoidosis.[30,18,31]

Different studies have evaluated the expression of KL-6 using immunohistochemistry.[17,22,32] KL-6 is moderately expressed in type II pneumocytes and respiratory bronchiolar epithelial cells and only weakly expressed in basal cells of the terminal bronchiolar epithelium of normal lung tissues. Type I pneumocytes, goblet cells, and mucous cells of the bronchial glands do not express KL-6. Ohtsuki et al. reported linear and continuous staining for KL-6/MUC1 on the cell surface of regenerating type II pneumocytes in patients with IPF or NSIP, but only discontinuous staining in normal lung tissues.[33–36] KL-6 is also strongly expressed in areas of destruction in the pulmonary structures, loose stroma and endothelial cells of lymphatic vessels, as well as the contents of these regions.[35] KL-6 is strongly expressed by atypical and regenerating type II pneumocytes in tissue sections obtained from patients with ILDs.[32,36,37] It also has strong expression in lung, pancreatic and breast cancer tissues. Weak to moderate expression was also observed in several other cancer tissues, such as stomach, colon and hepatocellular tumors.[38–40] KL-6 is also expressed in the premature lung during the early weeks of pregnancy and its expression persists even after lung maturation.[41,42]

Sarcoidosis and serum biomarkers

Sarcoidosis is a chronic systemic disorder characterized by non-caseating epithelioid cell granulomas and the accumulation of T-lymphocytes and macrophages in multiple organs.[3] The broncho-alveolar fluid level as well as serum level of KL-6 in patients with sarcoidosis is increased and significantly influenced by the severity of lung involvement.[18] Janssen et al. evaluated the ability of serum KL-6, SP-D and Clara cell 16(CC16) levels to discriminate between patients with sarcoidosis and control subjects and concluded that KL-6 was the best discriminative biomarker.[31] They also observed a trend in which the serum KL-6 levels were associated with disease severity and prognosis of pulmonary disease in the patients with sarcoidosis. In another study, Miyoshi et al. evaluated the significance of various biomarkers in patients with pulmonary sarcoidosis by measuring the serum levels of KL-6, serum amyloid A, soluble interleukin 2 receptor, lysozyme and angiotensin-converting enzyme.[43] These investigators demonstrated that KL-6 serum levels significantly correlated with the number of the total cells lymphocytes and CD4+ T lymphocytes in BAL fluid and were the single indicator of increased parenchymal infiltration in chest radiographs. A clinical cut-off value of 500 U/mL has been established for distinguishing patients with ILDs from healthy subjects and patients with lung diseases other than ILDs.[44] KL-6 serum levels higher than the cut-off value have been observed in more than 70% of patients with ILDs, including pulmonary sarcoidosis.

The primary cellular source of KL-6 in the affected lungs of patients with sarcoidosis is regenerating type II pneumocytes.[17,33] KL-6 is present in high concentration in broncho-alveolar lavage[23] KL-6 level in BAL fluid is significantly correlated with the total cell number, lymphocytes, neutrophils and albumin concentrations in BAL fluid and with serum KL-6 levels in patients with sarcoidosis. A correlation between KL-6 serum levels and albumin levels in BAL was also found in patients with chronic beryllium disease, suggesting the utility of serumKL-6 levels as a marker for the permeability of the air–blood barrier.[45] Both the destruction of the alveolar-capillary barrier and the enhancement of alveolar capillary permeability are thought to be necessary for the leakage of KL-6 into systemic circulation, since KL-6 is a high molecular weight glycoprotein. The increase in serum KL-6 levels in patients with sarcoidosis results from an increase in KL-6 production by regeneration of alveolar type II pneumocytes and/or enhancement of permeability following destruction of the alveolar–capillary barrier in the affected lung.

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Simultaneous measurement of the serum levels of KL-6, SP-A and SP-D in patients with sarcoidosis sometimes reveals a discrepancy between these serum markers. For instance, a transient increase in the serum levels of SP-A and SP-D following mild lung injury is frequently observed, while serum KL-6 levels remain unchanged.[10] This discrepancy suggests that increases in serum KL-6 levels do not reflect the intensity of inflammation, but rather indicate the extent of damaged alveolar epithelium and alveolar-capillary permeability. A study conducted by Honda et al suggested that thin-section CT findings of nodules, bronchial wall thickening, ground-glass opacity, traction bronchiectasis and architectural distortion were significantly more frequent in patients with elevated KL-6 levels than those with normal levels.[16] Altogether, these results strongly suggest that KL-6 is a useful marker for determining radiologic disease severity in pulmonary sarcoidosis.

Conclusion

In this review, we summarized the utility of KL-6 in the diagnosis of patients with sarcoidosis. The results from a number of researches investigating the biomarker KL-6 suggest that the serum levels of KL-6 are useful for detecting the presence of disease, evaluating disease severity and predicting the prognosis in the cases of Sarcoidosis. Since the measurement of serum KL-6 level is a rapid, reproducible, less invasive and easier to perform investigation than HRCT, BAL, Surgical lung biopsy and pulmonary function tests, this biomarker can provide a significant benefit to the clinical management of patients with Sarcoidosis. However, serum KL-6 alone is not sufficient to establish the diagnosis of Sarcoidosis. KL-6 is, thus, an add-on marker for the diagnosis and management of Sarcoidosis. The fundamental investigations like HRCT and Biopsy should also be preferred and serum biomarkers should be used as a supportive investigation. Though KL-6 has been used in clinical practice for more than ten years, evidence from clinical trials validating the clinical efficacy of KL-6 is yet to be proven. Further large and prospective studies are required to determine the clinical efficacy of KL-6 in the management of patients with Sarcoidosis.

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None

Conflict of interest

None

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