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Increased serum YKL-40 in patients with pulmonary sarcoidosis—a potential marker of disease activity?☆

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Summary *Background:* YKL-40, a growth factor for fibroblasts and vascular endothelial cells, is secreted by macrophages and neutrophils. Elevated serum YKL-40 is found in patients with diseases characterized by inflammation, tissue remodelling and ongoing fibrosis. The aim was to evaluate whether macrophages and giant cells in the granulomatous sarcoid lesions of patients with pulmonary sarcoidosis produce YKL-40 and to determine whether serum YKL-40 in these patients were associated with disease activity.

Methods: Serum YKL-40 was determined by radioimmunoassay in 27 patients with a histological diagnosis of pulmonal sarcoidosis. Immunohistochemical staining for YKL-40 antigen was performed in five biopsies with pulmonary sarcoid lesions. Serum YKL-40 was likewise measured in 173 healthy age-matched control subjects.

Results: Mononuclear cells/macrophages and giant cells in pulmonary sarcoid granulomas expressed YKL-40 protein. Serum YKL-40 was higher in patients with pulmonary sarcoidosis compared to controls ($P < 0.001$) and 63% had elevated serum YKL-40. There was a positive correlation between serum YKL-40 and serum

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angiotensin converting enzyme (rho = 0.55, $P = 0.0053$). Patients with serum YKL-40 > median value in the patient group had lower carbon monoxide diffusion capacity corrected for alveolar volume (D_LCO/VA) than patients with serum YKL-40 ⩽ the median value ($P = 0.015$).

Conclusions: Serum YKL-40 may be a novel biomarker of sarcoid disease activity and ongoing fibrosis in patients with pulmonary sarcoidosis.

Introduction

YKL-40*, a member of family 18 glycosyl hydrolases,[1–5] is a heparin and chitin-binding lectin[4,5] without chitinase activity.[1,5] The gene for YKL-40 is known[6] and located on chromosome 1, and its crystal three-dimensional structure has been described.[7] However, the site and mode of binding of YKL-40 to cell surface receptors is still unknown. The biological function of YKL-40 is not known in detail. One study has shown that YKL-40 is a growth factor for fibroblasts and acts synergistically with insulin-like growth factor 1 in stimulating the growth of fibroblasts.[8] YKL-40 is also a growth factor for chondrocytes and synovial cells,[9] is a chemo-attractant for endothelial cells and stimulates migration of these cells at a level comparable to basic fibroblast growth factor.[10] Furthermore, YKL-40 modulates vascular endothelial cell morphology by promoting the formation of branching tubules, indicating that YKL-40 may play a role in angiogenesis by stimulating the migration and reorganization of vascular endothelial cells.[10]

YKL-40 is secreted in vitro by activated neutrophils,[11] macrophages during late state of differentiation,[6,12,13] arthritic chondrocytes[1] and cancer cells.[14,15] In vivo YKL-40 is expressed by macrophages in inflamed synovial membrane[13,16,17] and atheromatous plagues[18] and by macrophages and giant cells in the media of arteritic vessels of patients with giant cell arteritis.[19] The pattern of YKL-40 expression in normal and disease states suggests that the protein plays a role in inflammatory processes, remodelling of the extracellular matrix and development of fibrosis. Elevated serum concentrations of YKL-40 are found in patients with rheumatoid arthritis,[2,17,20,21] giant cell arteritis,[19] inflammatory bowel disease,[22,23] bacterial infections,[24,25] liver fibrosis[26–28] and metastatic cancer.[29–32]

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by the formation of noncaseating epithelioid cell granulomas.[33] Although essentially all organs of the body may be affected by sarcoidosis, the lungs are the most commonly involved.[34] Disease activity is accompanied by chronic inflammation resulting in mononuclear cell infiltrates and formation of granulomas. Even in the early phase of granuloma formation, a fibrotic response may be observed. In some patients with sarcoidosis, the fibrotic response can produce substantial and irreversible organ dysfunction and remodelling. A significant fraction of patients with chronic active pulmonary sarcoidosis succumb to respiratory failure.

The natural course of sarcoidosis is unpredictable in the individual patient. In most cases pulmonary involvement clears or stabilizes in more than 80% of affected patients.[35] However, permanent severe pulmonary dysfunction may occur and accounts for most morbidity and mortality.[35] Many attempts have been made to find serological biomarkers of disease activity in pulmonary sarcoidosis, which could help identify patients at risk for irreversible organ damage, e.g. lung fibrosis. Since the early 1980's, measurement of serum peptidyl-dipeptidase A also known as serum angiotensin-converting enzyme (SACE) has been used routinely to monitor disease activity in patients with sarcoidosis.[36–38] In patients with sarcoidosis, ACE is produced predominantly in the epithelioid cells/macrophages in sarcoid granulomas.[39] Therefore, the SACE concentration reflects the total granuloma mass,[40] but is not useful as a prognostic parameter of significant irreversible organ dysfunction.[38]

The aim of the present study was threefold: Firstly, to evaluate whether mononuclear cells/macrophages and giant cells in sarcoid granulomas of patients with pulmonary sarcoidosis produce YKL-40. Secondly, to evaluate the distribution pattern of serum YKL-40 levels in patients with sarcoidosis. Thirdly, to search for an association between serum YLK-40 and disease activity.

Methods

Patients: The hospital records of 222 patients with a diagnosis of sarcoidosis who had been admitted to

*YKL-40 is also named: human cartilage glycoprotein-39 (HC gp-39),[1] 38-kDa heparin binding glycoprotein (Gp38k),[4] Chitinase 3-like protein (CHI3L1),[6,8] Breast regressing protein 39 kDa (brp-39),[15] and Chondrex.[20]