Lactic Dehydrogenase-Immunoglobulin Gk Complex in a Patient with Idiopathic Interstitial Pneumonia

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A female patient with idiopathic interstitial pneumonia (IIP) was admitted again 40 months after the diagnosis due to progression of clinical findings and increased activity of serum lactic dehydrogenase (LDH). Analysis of LDH isoenzyme disclosed a broad band between LDH4 and LDH5. Gel filtration and immuno-electrophoresis showed that immunoglobulin (Ig) G (k type) bound the LDH. With prednisolone and azathioprine, her symptoms and radiological findings improved concomitant with a decrease in the serum LDH activity. The LDH-IgGk complex disappeared in the circulation 14 months after initiation of the therapy. We report circulating LDH-Ig complex in a patient with IIP, which may be related to the disease progression of IIP. (Internal Medicine 35: 413-415, 1996)

Key words: lactic dehydrogenase (LDH) anomaly, interstitial pneumonia, steroid treatment, azathioprine

Introduction

Lactic dehydrogenase (LDH)-immunoglobulin (Ig) complex has been reported in various diseases (1). LDH-Ig complex might be associated with the pathophysiology of each disease since the complex disappears in the remission of some diseases (2). We describe circulating LDH-IgGk complex in a patient with idiopathic interstitial pneumonia (IIP). The complex appeared to be related to the progression of IIP in this case.

Case Report

A 63-year-old woman was admitted due to dyspnea on exertion in April 1990. She had finger clubbing, and fine crackles were present on chest auscultation. She had neither significant exposure to environmental agents, nor evidence of collagen diseases. Laboratory findings on admission included: leukocyte count, 8,800/mm³; red blood cell count, 378 x 10⁴/mm³; platelet count, 191 x 10³/mm³; and normal coagulation test. Erythrocyte sedimentation rate (ESR) was 48 mm/h. Serum LDH activity was 307 IU/l (normal range, 90-450 IU/l). Serum Ig levels were: IgG, 1,940 mg/dl; IgA, 421 mg/dl; and IgM, 217 mg/dl. Anti-nuclear antibody was ×40 with a speckled pattern: anti-DNA, anti-RNA and anti-ENA antibody were negative. Arterial oxygen tension (PaO₂) was 99.2 torr and arterial carbon dioxide tension (PaCO₂) was 44.8 torr. Chest X-ray showed reticulonodular shadow (Fig. 1a) and chest computed tomography (CT) (Fig. 1b) showed reticulonodular opacities and honeycombing distributed predominantly in subpleural regions. Pulmonary function tests showed no restrictive disturbance [total lung capacity (TLC), 3.1 l; %TLC, 91.3%; vital capacity (VC), 2.04 l; %VC, 95.3%; forced expiratory volume in one second (FEV₁,0), 1.64 l; FEV₁,0%, 80.8%]. However, a decrease of carbon monoxide diffusing capacity (%DLCO, 65.1%) was found. She was clinically diagnosed to have IIP since she did not wish to undergo any operative examinations.

In our outpatient clinic, her symptoms and findings on chest X-ray and chest CT gradually worsened, and serum LDH activity and ESR level were correspondingly elevated. She was admitted again to evaluate her pulmonary disease in June 1993. Laboratory findings on second admission showed higher levels of ESR (80 mm/h), IgG (2,337 mg/dl) and LDH activity (700 IU/l). Pulmonary function tests showed a restrictive disturbance pattern (TLC, 2.93 l; %TLC, 86.2%; VC, 1.54 l; %VC, 73.7%; FEV₁,0, 1.23 l; FEV₁,0%, 83.1%) and a lower level of %DLCO (58.1%), suggesting progression of IIP. A broad band between LDH4 and LDH5 isoenzyme was found in LDH isoenzyme analysis (Fig. 2). Gel filtration showed that LDH activity migrated to the G fraction which consisted of γ globulin group. Moreover, immuno-electrophoresis of the separated LDH
Figure 1. (a) Chest X-ray showing reticulonodular shadow.
(b) Chest computed tomography showing reticulonodular opacities and honeycombing distributed mainly in subpleural regions in bilateral lungs.

She had been observed without significant therapy. Her symptoms and radiological findings progressed with the gradual elevation of serum LDH activity and the ESR level. In April 1994, the LDH activity was 902 IU/l and the ESR level, 86 mm/h. We then administered azathioprine (40 mg daily) and prednisolone (7.5 mg daily) according to the therapeutic schedule by Raghu et al (3). Her symptoms and radiological findings gradually improved. In June 1995, serum LDH activity was 621 IU/l and ESR 34 mm/h. At that time, LDH isoenzyme analysis showed no abnormal band (LDH1, 24.1%; LDH2, 40.5%; LDH3, 20.6%; LDH4, 7.6%; LDH5, 7.2%).

Discussion

LDH is a tetramer molecule composed of two subunits, H and M (4). The molecular mass of the H and M subunits is 135 kD and 34 kD, respectively. There are five combinations of the H and M subunits, designated as LDH1 to LDH5. The fast moving, anodally migrating fraction is LDH1 and the most cathodally migrating fraction is LDH5. The three other isoenzymes are normally distributed between them (5). There have been several reports associated with LDH-Ig complex and disease condition (1, 2, 6–8). Under disease conditions, Ig classes and types of LDH-Ig complex are reported to be heterogeneous, and there are no specific patterns of LDH isoenzymes and Ig types in reported disorders. LDH-Ig complex was often observed in heart diseases and in collagen diseases. LDH is reported to be a marker of disease activity in several diseases including IIP (9). To our knowledge, however, there has been only one report on LDH-Ig complex in a patient with IIP (6).

In the present case, the serum LDH activity was within the normal limit at the time of diagnosis. As the lung disease had progressed, the serum LDH activity gradually became elevated. Circulating LDH-IgGκ complex was detected 40 months after the diagnosis of IIP. Interestingly, her symptoms and chest X-ray findings improved in parallel with a decrease in the LDH activity. The circulating LDH-IgGκ complex was not detected 14 months after initiation of therapy with prednisolone and
azathioprine. Serum LDH activity appeared to change in parallel with the disease progression of IIP. It was considered that LDH activity was influenced by LDH-IgG complex in this case since the development of LDH-IgG complex is known to increase LDH activity (10).

The LDH isoenzyme pattern in the normal human lung is: LDH1, 21%; LDH2, 23%; LDH3, 28%; LDH4, 18%; LDH5, 10% (10). In the present case, the LDH isoenzyme pattern of BAL fluid was in accordance with the LDH isoenzyme pattern in the lung. In LDH isoenzyme analysis, LDH-IgG complex in BAL fluid was not found. Accordingly, LDH-IgG complex was formed in the circulation, but it was not formed in the alveolar space. In IIP, LDH is released into the circulation from the damaged lung tissue, and the LDH meets immunoglobulins in the circulation. In this case, IgG type could specifically bind LDH. LDH-IgG complex is a large molecule with a molecular mass ranging from 285 kD (LDH1) to 690 kD (LDH5). It was reported that few molecules larger than 150 kD pass through the blood-gas barrier (11). This may be the reason why the LDH-IgG complex was not found in the BAL fluid of the present patient.

Several investigators (7, 12) speculated that LDH-Ig complex is formed with an antigen-antibody reaction since LDH binds to the Fab fragment of Ig. Fujita et al (8) reported that Ig does not bind LDH with an antigen-antibody reaction since the complex was dissociated by adding nicotinamide adenine dinucleotide. The means by which Ig binds LDH isoenzymes still remains unclear. The exact mechanism of the formation of LDH-Ig complex under disease conditions must be elucidated.

References