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Idiopathic Interstitial Pneumonia with Increased Serum Levels of Cancer-Associated Antigens, CA19-9 and SLX

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We report a case of idiopathic interstitial pneumonia (IIP) with elevated serum levels of carbohydrate antigen 19-9 (CA19-9) and sialyl Lewis^x-i (SLX). A 67-year-old Japanese woman was admitted to our hospital with a fever, dry cough and dyspnea on exertion. She had previously been admitted and had then been diagnosed as IIP. The serum level of SLX, measured by radioimmunoassay (RIA), was markedly elevated (120 U/mL; cut-off, < 38 U/mL). The serum level of CA19-9, measured by RIA, was at a slightly high level (46 U/mL; cut-off, < 40 U/mL). The values of CA19-9 and SLX were changed during her clinical course. These cancer-associated antigens were immunohistochemically expressed on the hyperplastic bronchiolar epithelium, on the surface epithelium cells of microscopic honeycombing and on exudates in air space. Repeated damage to the lungs may have forced these antigens of the markers into the blood circulation, which may have resulted in the elevated serum levels of CA19-9 and SLX observed in this patient.

Key words: CA19-9; cancer-associated antigen; idiopathic interstitial pneumonia; SLX

The cancer-associated antigens, carbohydrate antigen 19-9 (CA19-9) (Koprowski et al., 1979) and sialyl Lewis^x-i (SLX) (Fukushima et al., 1984), have been used as markers in the diagnosis of adenocarcinoma (Del Villano et al., 1983; Chia et al., 1985). Serum CA19-9 and SLX are, however, frequently elevated in patients with benign respiratory disease, such as cystic fibrosis (Frates et al., 1989; Wu et al., 1992), interstitial pneumonia (Bungo et al., 1988; Mukae et al., 1991), diffuse panbronchiolitis (DPB) (Noguchi et al., 1989; Mukae et al., 1993) and bronchiectasis (Burioka et al., 1995). We treated a female patient with idiopathic interstitial pneumonia (IIP) who had elevated serum levels of CA19-9 and SLX. We examined the serum levels of these tumor markers and the immunohistochemistry during her clinical course.

Case Report

A 67-year-old Japanese woman was admitted to our hospital in August 1995 with a fever, dry cough and dyspnea on exertion. She had previously been admitted because of an abnormality observed on a chest radiograph in January 1992. The diagnosis at that time was IIP. The patient had not received corticosteroid therapy.

Physical examination during present admission revealed fine cracking lung sounds and cyanosis. Her temperature was 38˚C. The laboratory examination revealed the following: leukocyte count, 8400/mm^3; a high level of lactic acid dehydrogenase (LDH, 307 IU/L, normal range, 100–225 IU/L); a high level of C-reactive protein (CRP), 3.6 mg/dL; and a high level of erythrocyte sedimentation rate (ESR), 122 mm/h. Serum levels of immunoglobulin G (3477 mg/dL), immunoglobulin A (481 mg/dL)

Abbreviations: CA19-9, carbohydrate antigen 19-9; CRP, C-reactive protein; DBP, diffuse panbronchiolitis; ESR, erythrocyte sedimentation rate; IIP, idiopathic interstitial pneumonia; LDH, lactic acid dehydrogenase; PaO_2, partial pressure of oxygen in arterial blood; RIA, radioimmunoassay; SLX, sialyl Lewis^x-i

and immunoglobulin M (320 mg/dL) were all elevated. Tests for anti-nuclear antibody and anti-DNA antibody were negative. A test for antibody against hepatitis C virus or human T-cell lymphotropic virus type I was negative. Mycobacterium in sputum culture was negative. Arterial blood gas analysis after breathing room air showed severe hypoxemia (PaO_2; 34 mmHg). The serum level of SLX, measured by radioimmunoassay (RIA), was markedly elevated (120 U/mL; cut-off, < 38 U/mL) and the serum level of CA19-9, measured by RIA, was slightly elevated (46 U/mL; cut-off, < 40 U/mL). The chest radiograph on admission showed reticular, small patches of infiltrate. Computed tomography of the chest demonstrated bilateral diffuse reticulo-nodular shadows in the lung fields. Gynecological examination and computed tomographic images of the head and abdomen revealed no malignancy.

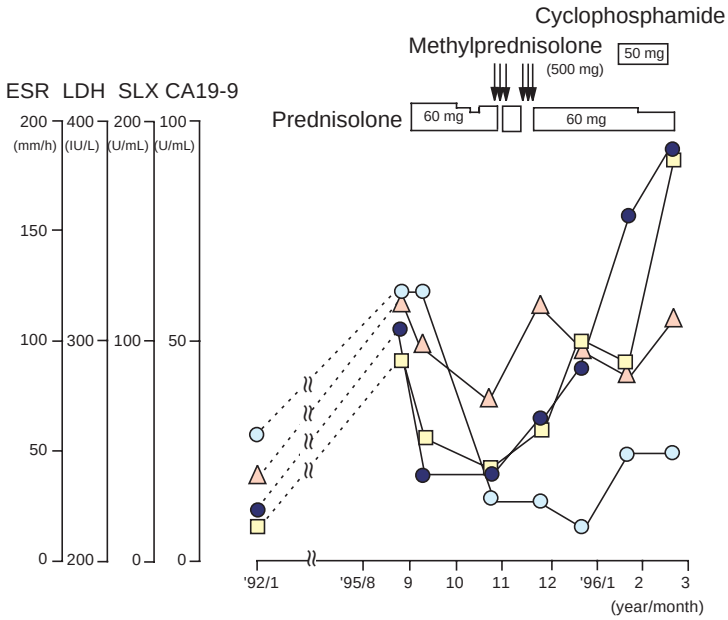

Fig. 1. Clinical course. ○, ESR; ●, LDH; △, SLX; □, CA19-9.

The patient's clinical course is summarized in Fig. 1. The IIP appeared to have been aggravated by infection in August 1995. So, the patient was administered antibiotics at that time. Nevertheless, her symptoms and hypoxemia did not improve. Because of the worsened condition of IIP, the patient was administered prednisolone (60 mg/day) intravenously in September 1995. An improvement in the PaO_2 (53 mmHg) of room air breathing was recognized. Reduction in the following parameters were noted: serum LDH (241 IU/L), ESR (28 mm/h), serum level of SLX (74 U/mL), and serum level of CA19-9 (21.4 U/mL) in October 1995. After an intravenous administration of methylprednisolone in November 1995, a respiratory infection was diagnosed. Cough and dyspnea on exertion were worsened. Oral cyclophosphamide (50 mg/day) was added to the regimen. The patient's condition deteriorated in February 1996; serum levels of LDH (389 IU/L), SLX (110 U/mL), and CA19-9 (94.3 U/mL) were again elevated. Mechanical ventilation was instituted, but the patient died in February 1996. There was a significant single linear correlation between the serum level of LDH and that of CA19-9 during this patient's clinical course (Fig. 2). However, there was no significant correlation between the serum level of LDH and that of SLX.

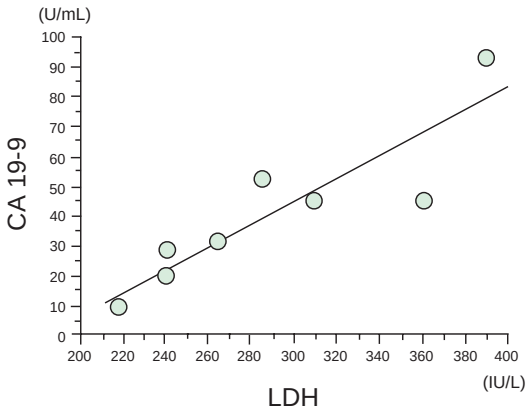

Fig. 2. Single linear correlation between the serum level of LDH and that of CA19-9 during this patient's clinical course. A significant correlation was observed ($r = 0.891$; $P < 0.003$).

Pathological findings

Specimens of tissue from the respiratory tract were obtained at necropsy. The lung exhibited a gross honeycomb appearance. Light microscopy showed dilatation of the bronchioles, a hyperplastic epithelium, severe fibrosis of the pulmonary parenchyma, anthracosis and infiltration of inflammatory cells (Fig. 3).

Immunohistochemical staining with anti-CA19-9 monoclonal antibody (1116-NS-19-9, TFB, Tokyo, Japan) showed negative reaction for CA19-9 on the lung specimen in January 1992 (Fig. 4a). Immunohistochemical staining with anti-SLX monoclonal antibody (Anti KM-93, Kyowa Medex, Tokyo) showed a positive reaction on the bronchiolar surface epithelium of the lung specimen in January 1992 (Fig. 4b). As for the necropsy specimen in February 1996, immunohistochemical staining with anti-CA19-9 and anti-SLX monoclonal antibodies showed strongly positive reactions for both CA19-9 and SLX on the hyperplastic bronchiolar epithelium, on the flattened and cuboidal metaplastic epithelial cells of microscopic honeycoming and on exudates in the air spaces (Figs. 4c and d). No malignant findings were recognized in the specimen of the patient's lung.

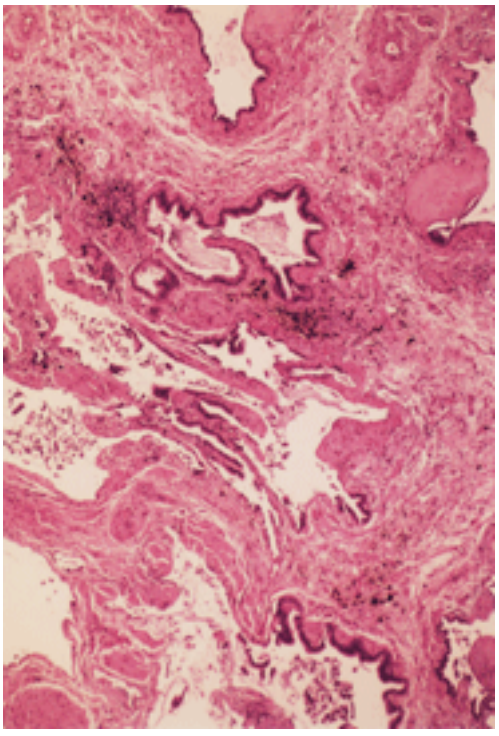

Fig. 3. Light microscopy showed a dilatation of the bronchioles, a hyperplastic epithelium, severe fibrosis of the pulmonary parenchyma, anthracosis and infiltration of inflammatory cells (hematoxylin and eosin stain, × 30).

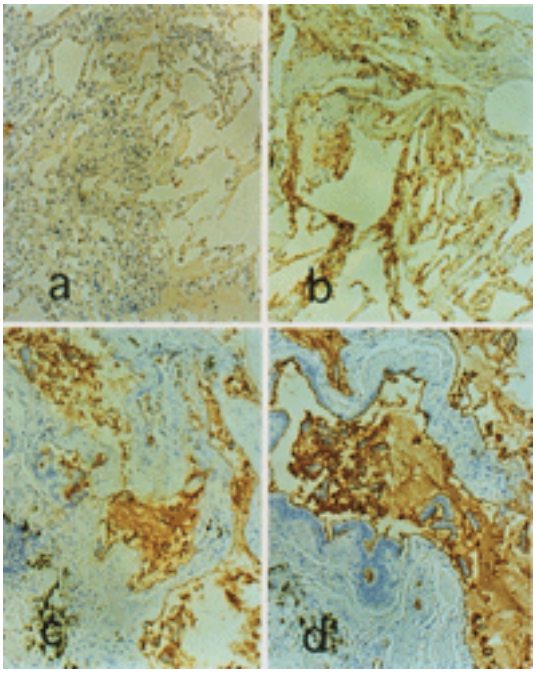

Fig. 4. a, b: Transbronchial lung biopsy specimen in January 1992. **c, d:** Necropsy specimen in February 1996.

a: Immunohistochemical staining with anti-CA19-9 monoclonal antibody showed negative reaction for CA19-9 (× 100). **b:** Immunohistochemical staining with anti-SLX monoclonal antibody showed positive reaction for SLX on the bronchiolar surface epithelium (× 100). Immunohistochemical staining with anti-CA19-9 and anti-SLX monoclonal antibodies showed strongly positive reactions for both CA19-9 (**c**) and SLX (**d**) on the hyperplastic bronchiolar epithelium, on the flattened and cuboidal metaplastic epithelial cells of microscopic honeycoming and on exudates in the air spaces (× 100).

Discussion

When the patient had only a slightly dry cough with slight abnormalities on the chest radiograph in January 1992, the serum levels of CA19-9 and SLX were within the normal range (Fig. 1). To verify whether CA19-9 and SLX were produced in the lungs, we examined immunohistochemically their localization in the lungs of this patient by an enzyme-labeled antibody method (Figs. 4a–d). In her deteriorating condition in August 1995, the serum levels of CA19-9 and SLX were both elevated (Fig. 1). As IIP worsens, these cancer-associated antigens are increasingly expressed on the surface of the bronchiolar epithelium and on the flattened and cuboidal metaplastic epithelial cells of microscopic honeycoming (Figs. 4c and d). CA19-9 is synthesized, to some degree, by the normal epithelial cells and respiratory glands of the airway (Atkinson et al., 1982; Matsuoka et al., 1990; Takayama et al., 1990), and SLX is also synthesized, to some degree, by the epithelial cells of the normal airway (Shiota et al., 1989) in healthy subjects. These sialylated glycoprotein tumor markers are immunohistochemically expressed in the mucus cells of bronchial hyperplastic glands and in the surface epithelium cells in patients with benign pulmonary diseases by inflammation (Noguchi et al., 1989; Mukae et al., 1991; Burioka et al., 1995). However, it has been unclear why these cancer-associated antigens are expressed on the lung tissue of patients with IIP. Repeated damage to the lungs may have forced these antigens of the markers into the circulation (Noguchi et al., 1989; Mukae et al., 1991; Mukae et al., 1993; Burioka et al., 1995), which resulted in elevated serum levels of CA19-9 and SLX in this patient. The serum level of SLX was within the normal range despite expression of SLX on the lung tissue in January 1992 (Fig. 2b). The destruction of the lung might be little at that time.

There was a significant correlation between the serum level of LDH and that of CA19-9 during this patient's clinical course. The serum level of LDH reportedly reflects damage to the lungs in interstitial pneumonia (De Remee, 1968). However, the serum level of LDH did not parallel the serum level of CA19-9 during December 1995 and January 1996. Although the mechanism is unclear, the expression of CA19-9 on the lung tissue might have been suppressed in January 1996. Treatment with a corticosteroid led to improvements in clinical symptoms and also led to reductions in serum levels of CA19-9, SLX, ESR and LDH. This finding seems to indicate that the administration of a corticosteroid transiently inhibited the exacerbation of IIP. When a high serum level of CA19-9 is recognized in IIP patients, the possibility remains that an examination of the correlation between serum values of LDH and CA19-9 during the clinical course may be beneficial to distinguish some IIP patients who had no malignant findings from the patients with adenocarcinoma.

Further study is needed to investigate why cancer-associated antigens are expressed in the lung tissue of the patient with IIP.

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