Association between CA 15-3 and progression of interstitial lung disease in a case of coexisting systemic sclerosis and recurrent breast cancer: A case report

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Abstract. Carbohydrate antigen 15-3 (CA 15-3) is known as a specific tumor marker for breast cancer, the main use of which is monitoring therapy in patients with advanced breast cancer. Either systemic sclerosis (SSc)-interstitial lung disease (ILD) or pulmonary arterial hypertension is currently the leading cause of disease-related morbidity and mortality in patients with scleroderma. Although CA 15-3 has been investigated as a biomarker in SSc-ILD, its role remains unclear. The current report presented a case of recurrent breast cancer diagnosed with SSc-ILD during treatment. The patient, at 63 years old, experienced shortness of breath with minimal exertion after four cycles of perutuzumab, trastuzumab and weekly paclitaxel. Computed tomography (CT) revealed ground-glass opacities and linear shadows in the peripheral lower lobes of both lungs. Although the development of lung involvement associated with breast cancer, such as carcinomatous lymphangitis, was initially suspected, because of the increase in CA 15-3, skin biopsies were taken from the left index finger base and extension side of the left elbow, which demonstrated increased thickness of the dermis, leading to a diagnosis of SSc-ILD. The findings in this case suggested the importance of considering a differential diagnosis, including ILD, concurrently while screening for the progression of recurrent breast cancer when encountering patients with breast cancer and elevated levels of CA 15-3.

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Abbreviations: CA 15-3, carbohydrate antigen 15-3; SSc, systemic sclerosis; ILD, interstitial lung disease; CT, computed tomography; PSL, prednisone; IVCY, intravenous cyclophosphamide; IPF, idiopathic pulmonary fibrosis; HE, hematoxylin and eosin

Key words: breast cancer, systemic sclerosis, interstitial lung disease, carbohydrate antigen 15-3

Introduction

Several tumor markers and biomarkers, both tissue- and serum-based, are currently used in the management of patients with breast cancer (1-4), among which, carbohydrate antigen 15-3 (CA 15-3) is considered a specific tumor marker for breast cancer. At present, the main utility of CA 15-3 is monitoring therapy in patients with advanced breast cancer, especially in women with non-evaluable disease. Most expert panels advise against the routine use of CA 15-3 in the surveillance of asymptomatic patients who have undergone surgery for breast cancer (5).

Systemic sclerosis (SSc) is a multi-system autoimmune disorder characterized by autoantibody production, endothelial damage with obliterative microvascular disease, inflammation, and fibrosis affecting the skin and internal organs (6,7). Cardiopulmonary involvement is a common manifestation in SSc, which presents as either interstitial lung disease (ILD) or pulmonary arterial hypertension (8), and is currently the leading cause of disease-related morbidity and mortality in patients with scleroderma (9). The most studied and characterized biomarker for ILD is Krebs von den Lungen 6 (KL-6) (10,11). CA 15-3 is the shed or soluble form of MUC-1 protein. MUC1 is strongly expressed by atypical and/or regenerating type II pneumocytes in tissue sections obtained from patients with ILDs (12-14). Although CA 15-3 has been investigated as a biomarker in SSc-ILD, its role remains unclear (15-17). Herein, we report a case of coexisting SSc and recurrent breast cancer who showed improvement in high CA 15-3 levels with amelioration of ILD without any systemic cancer treatment.

Case report

A 60-year-old woman underwent mastectomy with axillary lymph node dissection at JA Hiroshima General Hospital (Hatsukaichi, Japan) in October 2014 after preoperative chemotherapy (four cycles of docetaxel and trastuzumab, followed by four cycles of cyclophosphamide, epirubicin, and fluorouracil) for estrogen receptor-negative, HER2-positive right breast invasive ductal cancer, T2N1M0 stage IIB (18). Postoperative radiation therapy with 50 Gy in 25 fractions to the supraclavicular lymph nodes and chest wall was performed, followed by 14 cycles of 3-weekly trastuzumab.

At 63 years old, contrast-enhanced computed tomography (CT) performed as postoperative follow-up indicated brain metastasis in the right occipital lobe without liver, lung, or bone metastasis. She underwent γ-knife radiosurgery (20 Gy) followed by the administration of perutuzumab, trastuzumab, and weekly paclitaxel. After four cycles of perutuzumab, trastuzumab, and weekly paclitaxel, she experienced shortness of breath with minimal exertion, so the fifth course was canceled. CT revealed ground-glass opacities and linear shadows in the peripheral lower lobes of both lungs (Fig. 1). Although the development of lung involvement associated with breast cancer such as carcinomatous lymphangitis was initially suspected, because of the increase in CA 15-3, we investigated other possible causes of ILD (Fig. 2). From only CT image, the possibility of interstitial lung disease due to trastuzumab or pertuzumab cannot be ruled out (19). Bilateral sclerodactyly and facial skin thickness were found on clinical examination without a history of Raynaud's phenomenon and the finding of nail fold bleeding. A test for anti-nuclear antibodies with a nucleolar pattern was positive, at a titer of 1:320. Anti-double stranded DNA antibody, specific antibodies against centromere, SSA/SSB, Scl-70, RNP, and RNA polymerase III were negative. Pulmonary function tests showed a severely reduced %VC of 50.8%, indicating restrictive ventilatory impairment. Skin biopsies taken from the left index finger base and extension side of the left elbow demonstrated increased thickness of the dermis composed of broad and sclerotic collagen bundles extending to the underlying subcutis without inflammatory cell infiltration in hematoxylin and eosin stained-samples. These findings were consistent with the late stage of scleroderma (Fig. 3). From these findings, the diagnosis of SSc-ILD was made according to the diagnostic criteria for SSc proposed by the Ministry of Health, Labour and Welfare of Japan. The treatment for recurrent breast cancer was discontinued, and combination prednisone (PSL) (15 mg/day) and intravenous cyclophosphamide (IVCY) (500 mg/4 weeks) therapy was administered for induction treatment of SSc-ILD. PSL was tapered and discontinued at 1 year and IVCY was given five times in total. At 6 months after the start of treatment, her symptoms, including cough and dyspnea, had improved. CA 15-3 and KL-6 levels decreased simultaneously, reflecting the therapeutic effect (Fig. 2), and CT showed improvement in the ground-glass opacities in the peripheral lower lobes of both lungs as compared with those before treatment (Fig. 4). This patient is receiving treatment for SSc-ILD. The patient's SSc-ILD has not worsening and her breast cancer has not recurred despite not receiving treatment for four years.

Discussion

SSc is a devastating disease of unknown etiology that is characterized by systemic, immunological, vascular, and fibrotic abnormalities and a heterogeneous clinical course. Fibrosis, the hallmark of the disease, can affect the skin and internal organs, including lung (20). As is well known, pulmonary involvement is one of the most important features of SSc and often the leading cause of exitus. SSc-ILD is one of the most severe complications and is the main cause of SSc-related deaths (9,21); however, review of contemporary literature suggests improved survival among patients with SSc-ILD due to more aggressive monitoring and treatment (22,23). In clinical trials of SSc-ILD, change in forced vital capacity (FVC) is commonly used as a primary outcome measure, as low FVC predicts morbidity and mortality (24). Two landmark clinical trials, SLS-I (25) and SLS-II (26), established cyclophosphamide and mycophenolate mofetil as disease modifying therapies for SSc patients with active ILD.

The relationship between BC and SSc have been described previously (27-30). The standardized incidence ratio of BC in female SSc patients was found to be 1.62 (95% confidence intervals: 0.7-3.19) (31). many factors should be considered in the common pathogenesis of these two disorders (32). First of all, the female susceptibility observed for SSc suggests an influence of the same hormonal factors found to be involved in BC, such as elevated prolactin levels and decreased levels of dehydroepiandrosterone sulfate (33,34). Secondly, calcium channel blockers, a cornerstone treatment for SSc vasculopathy, have been suspected to be a risk factor for breast cancer in the general population (35-38). Lastly, several immunosuppressive drugs can be used in SSc but may contribute to cancer (39,40), whereas several chemotherapeutic agents (such as taxanes) and ionizing radiations have been associated with tissue fibrosis and/or scleroderma and may exacerbate pre-existing systemic scleroderma (41-45).

Taxanes, as well as other antineoplastic agents, have many toxic effects. Therefore, whether the etiology of the present case is drug-induced remains unclear. Taxane-induced scleroderma-like skin changes were first reported in 1995, and clinical characteristics include preceding edema, absence of Raynaud's phenomenon, and negative scleroderma-specific autoantibodies (46-49). The clinical course is refractory to treatment and commonly progressive even after discontinuation of the trigger drugs (50). However, unlike the present study, previous reports showed mainly skin disorders without ILD. In addition, the positivity of anti-nuclear antibodies with a nucleolar pattern in this case, which suggested the existence of SSc-specific antibodies against RNA polymerase III, Th/To, U3-RNP, and PM-Scl, helped us determine the diagnosis of SSc regardless of taxane exposure (51).

CA 15-3 is the shed or soluble form of MUC-1 protein. MUC1 is a transmembrane mucin with marked overexpression in human breast cancers as compared with that in normal

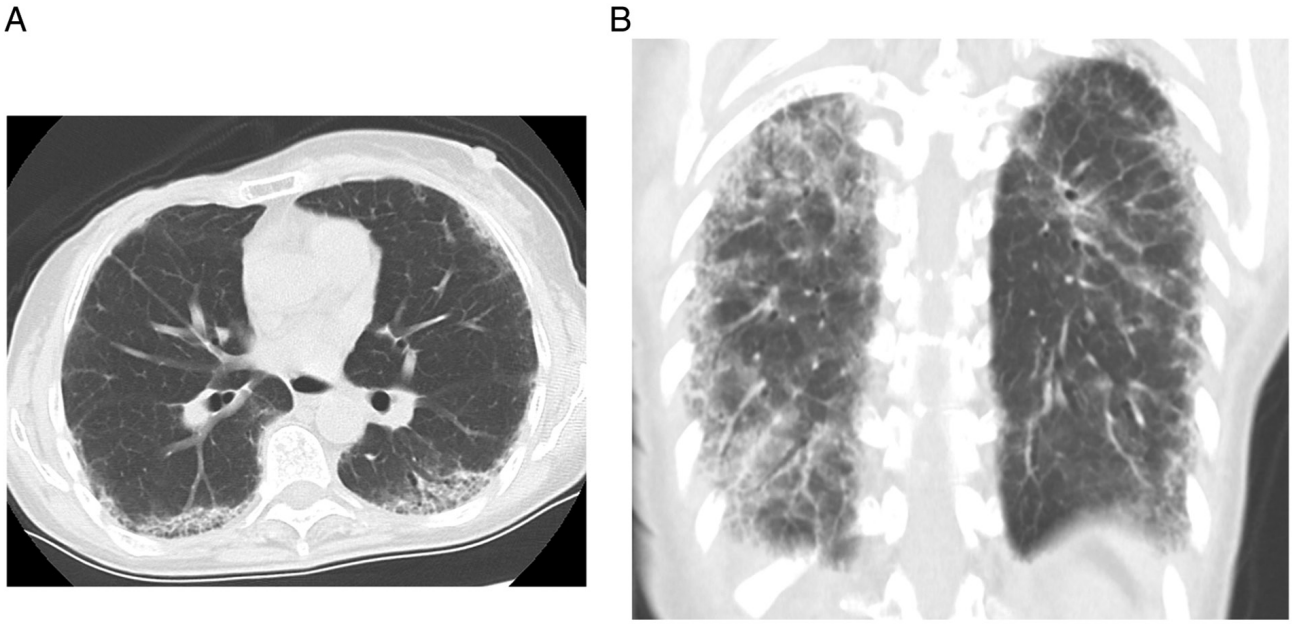

Figure 1. Chest computed tomography reveals ground-glass opacities and linear shadows in the peripheral lower lobes of both lungs. (A) Axial section view, (B) coronal section view.

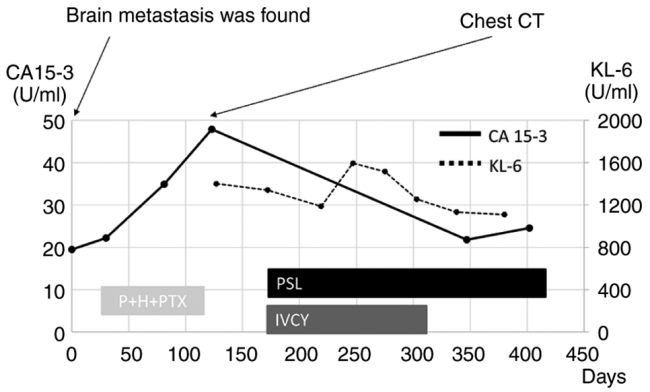

Figure 2. Changes in CA 15-3 and KL-6 from occurring brain metastasis. CA 15-3 and KL-6 decreased after treatment for systemic sclerosis-interstitial lung disease. CA 15-3, carbohydrate antigen 15-3; KL-6, Krebs von den Lungen 6; CT, computed tomography; P+H+PTX, perutuzumab, trastuzumab and weekly paclitaxel; PSL, prednisone; IVCY, intravenous cyclophosphamide.

ductal breast epithelial cells (52). On the other hand, MUC1 is strongly expressed by atypical and/or regenerating type II pneumocytes in tissue sections obtained from patients with ILDs (12-14). Serum levels of KL-6, an N-terminal subunit of MUC-1 protein, increases in the acute exacerbation of idiopathic pulmonary fibrosis (IPF). Serum levels of KL-6 correlate with IPF severity and prognosis (53). As both KL-6 and CA 15-3 exist in different positions of MUC1 (54), CA 15-3 may retain significant potential as an alternative biomarker for KL-6 in fibrotic lung diseases (16-18,55). In primary breast cancer, various studies have demonstrated that elevated serum CA15-3 values at diagnosis are associated with higher breast cancer stage, tumor size, positive axillary lymph nodes, and worse overall survival and disease-free survival (56-60). In metastatic breast cancer, CA15-3 was measured serially in a number of studies assessing their applications in early detection of disease progression and monitoring therapy response (61-65). On the other hand, CA15-3 was previously shown to be elevated in serum of SSc-ILD patients and was associated with severe ILD measured by fibrosis on HRCT, decreased FVC and DLCO and the presence of dyspnoea (16,66). In a study performed by Celeste *et al* on 221 SSc patients, among which 168 with ILD, CA15-3 serum levels were found to correlate with the extent of fibrosis detected on HRCT as well as to be predictive for progression-free survival, with progression being defined by a decline in either FVC or DLCO (17). The present study suggested that oncologists treating the patients with breast cancer should know CA15-3 is also associated with the condition of ILD. The concentration of some tumor-associated antigens (TAA) such as CA19-9 and CA125 were reported to be elevated in the sera of patients with SSc or systemic lupus erythematosus in comparison to healthy subjects (67). Because of public insurance coverage, the number of TAA for patients with breast cancer that could be measured at one time is limited. CEA could be measured for patients with breast cancer at the same time. In this patient, CEA did not show outlier or abnormal changes.

Meanwhile, KL-6 has been reported as a tumor marker in not only lung cancer, but also gastrointestinal, hepatic, pancreatic, and breast cancers (68,69). Kohno, the developer of KL-6 monoclonal antibody, noted that the serum levels of KL-6 mucin were elevated in patients with pulmonary, breast, and pancreatic adenocarcinomas (12). Elevation of KL-6 mucin in serum is significantly associated with the behavior of breast cancer (70) or lung cancer (68). Immunohistochemical analyses have clarified KL-6 mucin's clinicopathological significance in digestive organ cancer tissues. As the expression profile and clinicopathological significance of KL-6 mucin differ among each organ or

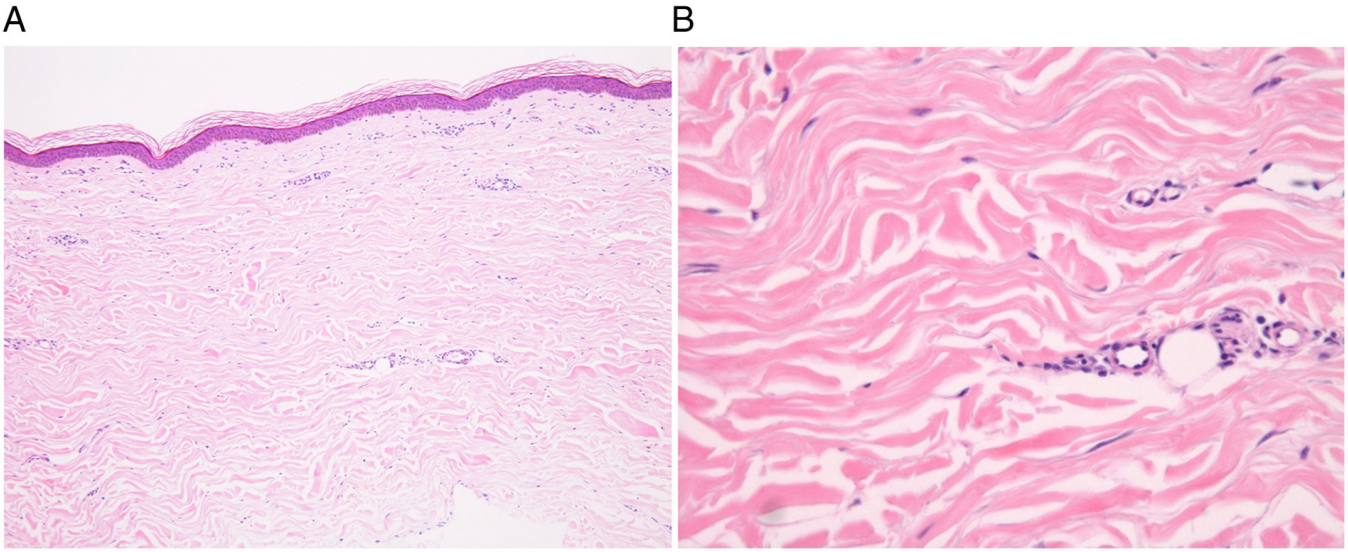

Figure 3. Histopathology of skin-punch biopsies from the left index finger base and extension side of the left elbow. The thickness of the dermis was composed of broad and sclerotic collagen bundles extending to the underlying subcutis without inflammatory cell infiltration. These findings were consistent with the late stage of scleroderma. (A) HE; magnification, x40. (B) HE; magnification, x400. HE, hematoxylin and eosin.

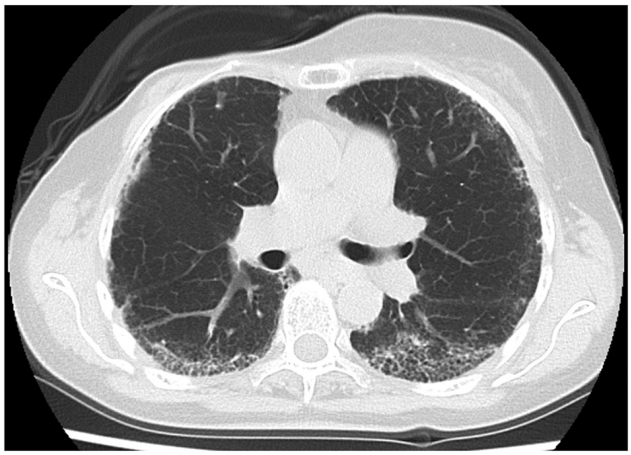

Figure 4. No progression of ground-glass shadows in the peripheral lower lobes of both lungs were seen on chest computed tomography compared with before treatment for sclerosis-interstitial lung disease.

disease, the biological role of KL-6 mucin might have a different importance in each location and state (68). Thus, the nature of KL-6 mucin remains unclear, and further investigations of KL-6 mucin in cancer are expected in the future.

In conclusion, serum levels of CA 15-3 correlated with the condition of SSc-ILD in a patient with recurrent breast cancer. This case suggests the importance of considering a differential diagnosis including ILD concurrently while screening for the progression of recurrent breast cancer when encountering patients with breast cancer and elevated levels of CA 15-3.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author's contributions

MO wrote the draft and critically revised the manuscript for important intellectual content. MO performed surgical and post-operative treatment. MO, YK, TS and KK contributed to the conception of the work, and interpreted and revised the results of the CT included in this report. YY treated the patient for SSc-ILD. YD diagnosed the disease pathologically. YY, SM, AT, AO, IN, MS, KI, MW, and YD collected and analyzed both the clinical laboratory and histopathological data. MO and YY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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