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Tumor-associated antigens in systemic sclerosis and systemic lupus erythematosus: Associations with organ manifestations, immunolaboratory markers and disease activity indices

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ABSTRACT

Background: Some tumor-associated antigens (TAAs) are expressed on inflammatory cells. We previously detected increased production of CA15-3, CA19-9 and CA125 in rheumatoid arthritis (RA). The production of some TAAs may also be increased in patients with systemic sclerosis (SSc), systemic lupus erythematosus (SLE) and other connective tissue diseases. Some of these TAAs contain sialylated carbohydrate motifs and they are involved in tumor-associated cell adhesion and metastasis.

Objectives: We assessed levels of TAAs in the sera of SSc, SLE patients, patients with infectious diseases and healthy subjects. Serum TAA levels were correlated with each other, as well as with disease activity markers and organ involvement.

Methods: TAAs including CEA, CA15-3, CA72-4, CA125 and CA19-9 were assessed by immunoassay in the sera of 92 patients with SSc, 40 patients with SLE, 50 age- and sex-matched healthy controls, as well as with 40 patients with current bacterial or viral infections. Normal upper limits for these TAAs were 3.4 mg/l, 25 kU/l, 6.9 kU/l, 35 kU/l and 34 kU/l, respectively.

Results: There were significantly more SSc patients showing abnormally high levels of CA19-9 (8.8% vs 2.0%), CA125 (11.0% vs 6.0%) and CA15-3 (28.4% vs 14.0%) in comparison to controls ($p < 0.05$). In SLE, significantly more patients had elevated levels of CEA (32.5% vs 20.0%), CA19-9 (7.5% vs 2.0%), CA125 (15.0% vs 6.0%) and CA72-4 (15.0% vs 8.0%) than did controls ($p < 0.05$). The mean absolute serum levels of CEA (6.6 ± 1.7 vs 1.8 ± 1.4 mg/l) and CA15-3 (22.9 ± 1.8 vs 18.6 ± 2.2 kU/l) were also significantly higher in SSc compared to controls ($p < 0.05$). We found numerous correlations between the serum levels of different TAAs within the SSc and SLE population. Among SSc patients, serum CEA ($R = 0.290$; $p = 0.005$), CA15-3 ($R = 0.260$; $p = 0.020$) and CA19-9 ($R = 0.257$; $p = 0.013$) correlated with renal involvement. Serum CA15-3 also correlated with joint involvement ($R = 0.329$; $p = 0.003$), ANA positivity ($R = 0.288$; $p = 0.010$) and CRP levels ($R = 0.407$; $p < 0.001$). Within the SLE population, serum CA72-4 correlated with central nervous involvement ($R = 0.624$; $p = 0.004$) and CA125 correlated with the SLEDAI composite activity index ($R = 0.666$; $p = 0.002$). Patients with infections exerted serum TAA patterns similar to healthy controls.

Conclusion: The concentration of some TAAs may be elevated in the sera of patients with SSc or SLE in comparison to healthy subjects. Pathogenically, most of these TAAs contain carbohydrate motifs and thus they may be involved in inflammation-associated adhesive events. Furthermore, the production of some TAAs may correlate with organ involvement or disease activity in scleroderma or lupus.

1. Introduction

Systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) are systemic connective tissue diseases involving multiple organs [1,2]. The follow-up of autoimmune patients including the determination of disease activity and prognostic markers is very

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important for the introduction of therapy, as well as for disease outcome [1–3].

Several complex scales and indices including clinical and laboratory markers have associated with disease activity and/or prognosis of SLE and SSc. In SLE, SLEDAI is a widely accepted composite disease activity marker [4] In SSc, disease activity cannot be easily defined due to the nature of the disease, therefore we regarded CRP as an activity marker in this disease.

A number of reports suggest that tumor-associated antigens (TAAs) may, apart from cancer cells, become expressed on the surface of inflammatory cells. A number of TAAs may play a role in the perpetuation of inflammation, some of them also serve as cell adhesion molecules (CAMs) [5–8]. Among these TAAs, the carcinoembryonic antigen (CEA; CD66) family consists of five members, CD66a–e. These TAAs belong to the immunoglobulin superfamily CAMs, they contain selectin-binding carbohydrate motifs, such as Lewis-x (Le-x) and sialyl-Lewis-x (sLe-x). Members of the CEA family are present on colorectal and gastric tumor [5,9–12]. In addition, CD66 antigens were described for the first time to be expressed on inflammatory leukocytes [5,11,13]. These molecules bind to E-selectin and they mediate the adhesion of tumor cells and neutrophils to activate endothelium during metastasis formation and inflammation, respectively [10,11,14]. We and others detected members of the CD66 family on neutrophils and monocyte/macrophages [5,11,15,16].

Among other TAAs studied in the present work, CA15-3 is expressed on breast carcinoma, CA19-9 on pancreatic carcinoma, CA125 on ovarian carcinoma, CA72-4 on gastric and mucinous ovarian carcinoma (Table 1). These TAAs may also act as CAMs. CA19-9, CA125 and CA15-3 contain carbohydrate motifs and these antigens are also involved in tumor cell adhesion. The antigenic determinant of CA19-9 is sialyl-Lewis-a (sLe-a). sLe-a as well as sLe-x is selectin ligands [17]. CA125 (MUC16) is a giant mucin-like glycoprotein, which mediates ovarian cancer cell adhesion [7]. CA15-3, also termed MUC1, is involved in breast cancer metastasis [8]. In addition, CA15-3 mediates transendothelial tumor cell migration by ligating endothelial intercellular adhesion molecule-1 (ICAM-1) [18].

TAAs may also be detected in the sera and tissues of autoimmune patients [5–8,19–24]. We and others reported an increased expression of CD66 antigens in RA synovial tissues compared to normal synovia [5,15]. We have recently found increased production of circulating CA19-9, CA15-3 and CA125 in RA compared to healthy subjects. Moreover, serum CEA levels correlated with IgM rheumatoid factor concentrations [24]. Serum CA19-9 levels may be increased in SSc [20], primary Sjögren's syndrome [6,23], mixed connective tissue disease (MCTD) [6], polymyositis [6], as well as RA [19,24]. In SSc and SLE, abundant CA125 release has been associated with pleural effusion [20,22]. Serum CA15-3 levels were higher in SSc patients with severe lung involvement [21]. Yet, little information is available on the association of TAAs described above and SSc or SLE.

In this study, we assessed serum TAA levels in SSc and SLE patients in comparison to healthy controls. TAA production in autoimmune patients was also correlated with disease activity scores and/or organ manifestations.

Table 1
Tumor-associated antigens

	Molecular weight (kDa)	Function	Associated cancer	Normal laboratory upper limits
CEA (CD66, sialyl-Lewis-X)	180	Adhesion	Colon, pancreas, lung	<3.4 mg/l
CA15-3 (MUC1)	300–450	Adhesion	Breast	<25 kU/l
CA19-9 (sialyl-Lewis-a)	250	Adhesion	Colon, pancreas, biliary	<34 kU/l
CA125 (MUC16)	200	Adhesion	Ovary	<35 kU/l
CA72-4	400		Gastrointestinal, ovary, lung	<6.9 kU/l

2. Patients and methods

2.1. Patients and controls

Altogether 92 SSc and 40 SLE patients were included in the study. SSc patients consisted of 78 women and 14 men. Their mean age was 50.2 ± 8.7 years (range: 32–70 years). Regarding subgroups, 61 patients had lcSSc and 31 the diffused form (dcSSc). We included 34 female and six male SLE patients. Their mean age was 42.4 ± 11.7 years (range: 22–68 years). Fifty healthy blood donors served as controls (41 women and nine men; mean age: 54.5 ± 9.3 years; range: 43–79 years). In order to compare autoimmune patients to patients with infectious diseases, we also assessed 40 patients (35 females and five males; mean age: 49.2 ± 8.8 years) with ongoing bacterial or viral infections including pneumonia, mononucleosis, influenza, cholecystitis, pyelonephritis and bronchitis. The diagnosis of SSc and SLE was established using the standard ACR criteria [1,2]. None of the autoimmune patients or controls ever had any malignancies. In addition, all patients or controls with increased serum TAA levels were further assessed by clinical sign analysis, chest X-ray, abdominal ultrasound, general laboratory analysis, as well as, if necessary, mammography or endoscopy in order to exclude underlying malignancies. Also, concurrent infections were excluded by clinical analysis, laboratory tests and, if needed, more detailed examinations and cultures. Clinical manifestations including joint involvement (primarily arthralgia and joint deformities in SSc and polyarthritis in SLE), Raynaud's phenomenon, skin, pulmonary or renal involvement were assessed by physical examination and standard imaging techniques (X-ray, abdominal ultrasound, chest CT and HRCT). Kidneys were assessed by ultrasound, urinary sediment was also analyzed and, if needed, kidney biopsy was performed. Serum samples were obtained from all patients and controls. Institutional Ethical Committee approval was obtained for this study.

2.2. Determination of serum tumor antigen concentrations

TAAs including CEA, CA19-9, CA15-3, CA125 and CA72-4 were determined by electrochemiluminescence immunoassays using the Modular E170 automated analyzer (Roche, Basel, Switzerland), according to the manufacturer's instructions (Table 1). The normal upper limit for these TAAs, determined by the manufacturer, were as follows: CEA: 3.4 mg/l, CA19-9: 34 kU/l, CA15-3: 25 kU/l, CA125: 35 kU/l, and CA72-4: 6.9 kU/l. All SSc, SLE and normal sera were assayed for these TAAs, and the percentage of "positive" patients (values above the upper limit) as well as the absolute values of serum concentrations was compared. In addition, absolute TAA concentrations in the sera of autoimmune patients were correlated with the presence or absence of a certain organ involvement described above, as well as with immunolaboratory markers discussed later. In correlation studies, patients with values above or below the upper or lower cutoff were excluded.

2.3. Assessment of immunolaboratory markers

In SSc, ANA, anti-Scl70 and anti-centromere autoantibody levels, while in SLE, anti-dsDNA and anti-cardiolipin IgG autoantibody levels were assessed by standard techniques. Serum CRP levels were assessed by quantitative nephelometry (Cobas Mira Plus – Roche; reagents: Dialab). CRP values $\geq$5 mg/l were regarded as positive.