Rheumatoid arthritis: correlation between rheumatoid factor levels and CA-125 tumour marker elevation

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Rheumatoid factors (RFs) are autoantibodies directed against the Fc portion of IgG. Tumour markers (eg, CA-125, CA-19-9) are tumour-expressed proteins that are usually measured in the serum by means of ELISA sandwich assays, in which murine monoclonal antibodies are used to capture the circulating antigen under investigation.¹⁻³

Given the extensive homology between the Fc regions of murine and human IgG antibodies, it may not be unexpected that anecdotal reports have shown that tumour markers can be falsely increased in the presence of human antimouse antibodies or RFs.⁴⁻⁶ We systematically sought to determine whether patients with active RF-positive rheumatoid arthritis (RA) and no evidence of a neoplastic disorder could have "falsely" increased levels of some commonly tested serum tumour markers.

A total of 53 patients (45 women and 8 men; median (range) age 51 years (23-58)) fulfilling the American Rheumatology Association diagnostic criteria for RA were included in the present study. Patients with other autoimmune or inflammatory diseases associated with increased RF titres were excluded. Data for the following variables were collected: RF (measured by latex agglutination test; normal value ≤ 15 IU/ml), CA-125 (measured by ELISA; normal value ≤ 33 U/ml), carcinoembryonic antigen (CEA; measured by ELISA; normal value ≤ 5 ng/ml) and CA-19-9 (measured by ELISA; normal value ≤ 37 U/ml). Patients were monitored for the development of cancer over a 3-year period.

Interestingly, 7 (13.2%) patients had high values of CA-125, 2 (3.8%) patients had increased CEA and 1 (1.9%) patient had a high value of CA-19-9. Table 1 summarises the measurements of tumour markers among the study patients. No significant correlation was detected between RF titres and levels of CEA, CA-125 and CA-19-9 (data not shown). Of note, none of the patients included in the present study developed cancer during the follow-up period.

From a theoretical point of view, the detection of RF in the serum equals the presence of Fc fragment-reacting antibodies that can potentially "bridge" the mouse monoclonal antibodies used to capture the particular serum antigen (tumour marker), and potentially yield a false-positive increase in the tumour antigen by ELISA reading. In particular, the high levels of IgM RFs observed in RA may cross-react with mouse monoclonal or polyclonal antibodies in the in vitro assays and probably cause falsely increased tumour marker levels.

Even though our study had a small sample size, lacked a control group and did not show a formal statistical correlation of RF titre and CA-125 levels, the fact that approximately 15% of patients with RA had a false-positive increase of CA-125 implies that extreme caution is required in the interpretation of positive tumour markers (especially CA-125) in patients with RA. Moreover, this may help physicians to avoid misdiagnoses, unnecessary diagnostic investigations or unfortunate therapeutic decisions.⁷ Finally, it is expected that future research on the detection of tumour markers will lead to the development of methods that will overcome RF binding by eliminating these autoantibodies from patients' serum, or by applying antibodies of different origin or antibody fragments (eg, F(ab)₂) in the assay.

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Abbreviations: CEA, carcinoembryonic antigen; RA, rheumatoid arthritis; RF, rheumatoid factor

Table 1 Tumour marker measurements among patients with rheumatoid arthritis

Tumour markers	Falsely increased n (%)	Median value	Minimum value	Maximum value
CA-125 (cut-off 33 U/ml)	7 (13.2)	8.0	0.5	530.0
CEA (cut-off 5 ng/ml)	2 (3.8)	1.0	0.1	30
CA-19.9 (cut-off 37 U/ml)	1 (1.9)	7.9	0.2	54.2

CEA, carcinoembryonic antigen.