

Tumor Antigen Markers for the Detection of Solid Cancers in Inflammatory Myopathies

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Abstract

Dermatomyositis and polymyositis patients have an increased risk of developing cancers. We have assessed the diagnostic values of serum tumor markers for the detection of solid cancer in dermatomyositis/polymyositis patients. Serum carcinoembryonic antigen, CA15-3, CA19-9, and CA125 were assayed by immunoradiometric methods in 102 dermatomyositis/polymyositis patients. All the patients had complete physical examination, chest X-ray, echocardiogram, gastrointestinal tract endoscopic explorations, thoracoabdominopelvic computed tomography scan, and all women had gynecologic examination and mammogram. Exclusion criteria for study were childhood dermatomyositis, inclusion body myositis, myositis associated with a connective tissue disease, prior history of cancer, and the presence of benign conditions known to elevate serum tumor markers. After a median follow-up of 59 months, 10 (9.8%) patients had a solid cancer. Initial elevation of CA125 was associated with an increased risk of developing solid cancer [$P = 0.0001$ by Fisher's exact test; odds ratio (OR), 29.7; 95% confidence

interval (95% CI), 8.2-106.6]. For CA19-9, there was a trend towards a significant association ($P = 0.007$; OR, 4.5; 95% CI, 1-18.7, respectively). Diagnostic values of elevated CA125 and CA19-9 at screening increased when the study analysis was restricted to patients who developed a cancer within 1 year ($P < 0.0001$ and $P = 0.018$, respectively) or to patients without interstitial lung disease ($P = 0.00001$; OR, 133; 95% CI, 6.5-2733 and $P = 0.027$; OR, 9; 95% CI, 1.5-53, respectively). Individual comparisons of the baseline and the second CA125 value showed that three of the eight patients with cancers versus 3 of the 76 patients without, displayed an increase of their CA125 level ($P = 0.01$ by Fisher's exact test). We conclude that CA125 and CA19-9 assessment could be useful markers of the risk of developing tumors for patients with dermatomyositis and polymyositis and should therefore be included in the search for cancer in dermatomyositis/polymyositis patients, especially for patients without interstitial lung disease. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1279-82)

Introduction

Meticulous epidemiologic studies have shown an increased rate of cancer in dermatomyositis and polymyositis (1-3). Although a great diversity of malignancies may be observed in dermatomyositis/polymyositis, leading sites are ovary, bronchi/lung, gastrointestinal tract, and breast (2, 3). Most of these solid cancers can be occult. How the search for these neoplasia should be conducted is still a matter of debate (4-6). Two opposing attitudes exist regarding the extent of the explorations for malignancy in dermatomyositis/polymyositis (5). One proposal is restricted to patient interrogation, complete physical examination, few routine blood and urine tests, fecal occult blood, chest X-ray, and additional oriented examination in case of specific symptoms or signs. The other attitude includes besides the preceding exams, a thoracoabdominopelvic computed tomography (CT) scan, gastrointestinal tract, and bronchial tree endoscopic explorations, mammogram, bone marrow biopsy, study of circulating lymphocyte subpopulations, and serum immunoelectrophoresis. Screening for the main serum tumor markers is sometimes included in the latter attitude (5, 7, 8). Indeed, although the value of tumor markers in the detection of cancer is controversial and search

for these markers are not recommended as a screening test for many cancers in the general population by guidelines (9, 10), the higher incidence of malignancy observed in dermatomyositis/polymyositis patients suggests that the diagnostic values of these tests might increase in this limited group of patients (10). However, the usefulness of these tumor markers for the detection of solid cancers in dermatomyositis/polymyositis has never been evaluated.

We have assessed the diagnostic values of carcinoembryonic antigen (CEA), carbohydrate antigen-125 (CA125), carbohydrate antigen 19-9 (CA19-9), and carbohydrate antigen 15-3 (CA15-3) assays for the detection of solid cancers in a group of dermatomyositis/polymyositis patients.

Materials and Methods

The study was a historical cohort. All the patients were seen at the Service de Médecine Interne, Hôpital Pitié-Salpêtrière, Paris, France. All had a diagnosis of polymyositis and dermatomyositis based on the criteria from Bohan and Peter (11): symmetrical muscle weakness, increased serum muscle enzymes, myopathic changes on electromyography, with typical histologic findings on muscle biopsy, and characteristic dermatologic manifestations (heliotrope rash, periungual erythema, Gottron papules, and poikiloderma) for dermatomyositis. All the patients had a muscle biopsy.

Screening included patient interrogation, complete physical examination, chest X-ray, gastrointestinal tract endoscopic explorations, thoracoabdominopelvic CT scan including

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contrast-enhanced images, gynecological examination and mammogram in women, and determination of tumor antigen serum levels (see below). Echocardiogram was done systematically.

All the cancers were confirmed by histopathologic examination and the date of this examination was considered as the date of the cancer diagnosis. We only considered solid cancers and did not take into account hematological malignancies because the tumor antigens studied here are poorly relevant for their screening.

The date of the muscle biopsy was considered as the beginning of the study. The end of follow-up has been set up at April 15, 2002. All living patients and/or their general practitioner have been contacted by phone and questioned about cancer occurrence.

Patients who had one of the following conditions were excluded from the study:

- patients with inflammatory myopathies which carry a known or supposed low risk of developing malignancies (refs. 1, 11-15; i.e., childhood dermatomyositis, dermatomyositis onset <15 years), inclusion body myositis, myositis associated with a defined connective tissue disease such as systemic lupus erythematosus or scleroderma, and myositis occurring as a feature of mixed/undifferentiated connective tissue disease.
- patients with solid cancer within 5 years before the tumor antigen determinations
- patients with serous effusion, a known condition of CA-125 elevation (16), on thoracoabdomino-pelvic CT scan and/or echocardiogram,
- patients with benign liver diseases, cholelithiasis, and uncontrolled diabetes (i.e., nonmalignant diseases known to elevate CA19-9, CA125, and CA15-3; ref.17).

Myositis-Associated Interstitial Lung Disease. Interstitial lung disease (ILD) was diagnosed by chest high-resolution CT which allows early identification (18, 19). Cardiac failure that can give linear opacities of the lung was ruled out by clinical examination and echocardiogram.

Tumor Marker Assays. Serum CEA, CA15-3, CA19-9, and CA125 were assayed by immunoradiometric methods using the following kits (Abbott AxSYM, Rungis, France). Threshold values given by the manufacturer were 5 ng/mL, 25, 35, and 37 units/mL for CEA, CA15-3, CA125, and CA19-9, respectively. Tumor antigen levels were usually assessed at time of muscle biopsy and never later than 100 days after.

Statistical Analysis. Data analysis was done on SAS (Statistical Analysis System, SAS Institute, Inc., Cary, NC). A χ^2 test or a Fisher's exact test has been used to compare proportions, and a 95% confidence interval (95% CI) has been computed for each odds ratio (OR) when applicable. A Wilcoxon rank sum test has been computed for ordinal variables.

Results

Patients and Cancers. One hundred and two patients, 64 women (mean age, 53 ± 15.5 years) and 38 men (mean age, 49 ± 14 years) were included in the study. Diagnosis of dermatomyositis and of polymyositis was made in 50 (31 women, 19 men) and 52 (33 women, 19 men) patients, respectively. The median of follow-up was 59 months (range, 2-208). Five patients (4.9%) were lost to follow-up after 14, 16, 26, 40, and 61 months. Among the 102 dermatomyositis/polymyositis patients, 10 (9.8%) developed a solid cancer, five had a dermatomyositis, and five had a polymyositis. Mean age of patients with cancers was 56.6 ± 12.6 years. The median of follow-up for these patients was 10.4 months (range, 0.7-165). Six cancers were diagnosed during the first year, one during the second year and three after the seventh year after muscle biopsy (for details, see Table 1).

Diagnostic Values of Tumor Markers in Inflammatory Myopathy Patients

Carcinoembryonic Antigen. Four of the 102 inflammatory myopathy (3.9%) patients had a screening CEA level higher than the threshold value (5 ng/mL). None of these four patients developed a solid cancer ($P = 0.9$, Table 2; OR, 1; 95% CI, 0.05-18.6).

CA15-3. Among the 102 patients assessed for CA15-3 levels at screening, 22 (21.8%) were positive. Two of these patients (9.1%) developed a solid cancer ($P = 0.9$, Table 2; OR, 0.9; 95% CI, 0.17-4.5).

CA19-9. Eleven of the 102 inflammatory myopathy patients (11.7%) had an elevated CA19-9 level. Three subsequently developed a solid cancer ($P = 0.07$, Table 2) within 1 year after screening (4.1, 4.3, and 10.5 months). OR was 4.5 (95% CI, 1-18.7) for all the patients, 4.2 (95% CI, 0.58-30.7) for dermatomyositis patients, and 5.6 (95% CI, 0.41-76.4) for polymyositis patients. Positive (PPV) and negative predictive value (NPV) of increased screening CA19-9 were 27.3% and 92.2%, respectively.

Table 1. Initial serum tumor markers in the 10 DM/PM patients who subsequently developed a solid cancer

Patient	Gender	Diagnosis	Age at diagnosis (y)	Time interval (mos)	Type of cancer	CEA ($n < 5$ ng/mL)	CA15-3 ($n < 25$ units/mL)	CA19-9 ($n < 37$ units/mL)	CA125 ($n < 35$ units/mL)
1	F	DM	62	4.3	Cholangiocarcinoma	1.6	61	168	171
2	F	DM	57.6	4.1	Peritoneal papillary	0.7	529	723	4,360
3	F	DM	45.5	90.3	Ovarian	0.5	15	10	167
4	F	DM	70.9	20.9	Lung large cell carcinoma	3.1	13	8	13
5	M	DM	57.8	10.3	Gastric adenocarcinoma	3	6	0.5	4
6	M	PM	44.4	165.1	Renal carcinoma	1	12	7	7
7	M	PM	35.5	10.5	Lung adenocarcinoma	1.6	14	68	189
8	M	PM	58	100.2	Lung adenocarcinoma	0.5	10	31	10
9	M	PM	78.2	0.7	Rectum adenocarcinoma	0.5	15	30	41
10	M	PM	56	1.2	Lung large cell carcinoma	2.7	4	1.8	11

NOTE: Time interval is the time between muscle biopsy and pathologic diagnosis of cancer. Tumor markers were assessed at the time of muscle biopsy. n = threshold values. Values in bold type are over the threshold. Abbreviations: F, female; M, male; DM, dermatomyositis; PM, polymyositis.

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Table 2. Diagnostic values of tumor markers in patients with inflammatory myopathies

	No. patients with all patients (n = 102)	Increased tumor patients with cancer (n = 10)	Marker levels patients without cancer (n = 92)	P	Solid cancer OR (95%CI)	P'
ACE	4	0	4	0.9	1 (0.05-18.6)	0.9
CA15-3	22	2	20	0.9	0.9 (0.17-4.5)	0.6
CA19-9	11	3	8	0.07	4.5 (1-18.7)	0.018
CA125	8	5	3	0.0001	29.7 (8.2-106.6)	<0.0001
CA19-9 + CA125	3	3	0	0.0007	86.3 (4.06-1,832)	<0.0001

NOTE: *P* for comparison between patients with and without cancers during the whole study period, by Fisher's exact test. *P'* for comparison between patients with and without cancers within 1 year after the screening, by Fisher's exact test.

CA125. CA125 levels were assessed over the threshold 8 (7.8%) patients; out of whom five developed a cancer ($P = 0.0001$, Table 2). In four of these five patients, the cancer occurred within 1 year after the screening evaluation of CA125 (0.7, 4.1, 4.3, and 10.5 months). OR was 29.7 (95% CI, 8.2-106.6) for all the patients, 66 (95% CI, 4.6-953) for dermatomyositis patients, and 15 (95% CI, 1.5-147) for polymyositis patients. PPV and NPV of increased screening CA125 were 62.5% and 94.7%, respectively.

CA19-9 and CA125. CA19-9 and CA125 combined together were increased in 3 patients. All three patients developed cancer ($P = 0.0007$). The risk of cancer was considerably higher compared with patients with normal values of these two markers (OR, 86.3; 95% CI, 4.06-1832). PPV and NPV of increased CA19-9 and CA125 were 100% and 92.9%, respectively.

Diagnostic Values of Tumor Markers for Inflammatory Myopathy Patients with Cancers Diagnosed within 1 Year after the Screening. When the study analysis was restricted to patients who developed a cancer within 1 year after the screening (6 of 10), the diagnostic value of both CA19-9 and CA125 increased ($P = 0.018$ and $P < 0.0001$, respectively; Table 2).

Longitudinal Variations of CA19-9 and CA125. We next try to know whether there were variations in CA19-9 and CA125 levels in patients with and without cancers. Sera obtained during the inflammatory myopathy follow-up, 3 to 6 months after the screening assessment, were frozen and thawed for a second determination of CA125 and CA19-9 levels. At second assessment, all the three patients (100%) with a screening elevated CA19-9 who subsequently developed a cancer exhibited an increase of CA19-9 (168-200, 723-837, and 68-208 units/mL). All the eight patients with initial elevated CA19-9 but without cancer had a decrease of the CA19-9 under the threshold.

Among the five patients with cancer and increased CA125 at screening, four could be assessed a second time; the other had a cancer 0.7 month after inflammatory myopathy diagnosis and was not further assessed. Three of these four patients had a raise of CA125 (171-217, 189-228, and 4,360-8,620 units/mL). These three patients had a cancer diagnosed within 1 year after the screening (4.1, 4.3, and 10.5 months after the screening test, respectively). One patient with cancer had a stable tumor antigen level (167-164 units/mL) at second CA125 determination. His cancer was diagnosed 90.3 months after the screening. For the three patients without cancer and with elevated screening value, the CA125 level returned to reference range at second determination.

To allow statistical comparisons, 73 additional patients without cancer were assessed 3 to 6 months after the initial evaluation. Individual comparisons of the baseline and the second CA125 value, showed that 3 of the 76 patients without cancers (73 without and 3 with increased CA125 at screening) displayed an increase of their CA125 level, which remained within the reference range, versus three of the eight patients with cancers ($P = 0.01$).

Effect of the Presence of Diffuse Interstitial Lung Disease on the Diagnostic Values of CA19-9 and CA125. One of the possible features of inflammatory myopathy is the presence of ILD. The presence of ILD is negatively associated with risk of cancer (20, 21). In a previous study (22), we have shown that ILD is by itself a cause of elevation of tumor antigen. We have studied the effect of the presence of myositis-associated ILD on the diagnostic values of CA19-9 and CA125. Twenty-six patients had ILD. The median follow-up of these patients was 37.9 months (range, 2.3-138) and was not different from the one of patients without ILD (63.3; range, 2-207; $P = 0.10$ for comparison by Wilcoxon rank sum test). None of the 10 patients who developed a cancer had ILD ($P = 0.06$). In the 76 inflammatory myopathy patients without ILD, both increased CA19-9 and/or CA125 at screening were associated with an increased risk of cancer ($P = 0.027$; OR, 9; 95% CI, 1.5-53 and $P = 0.00001$; OR, 133; 95% CI, 6.5-2733, respectively). In the subgroup of patients without ILD, CA19-9 PPV and NPV were 50% and 90% and CA125 PPV and NPV were 100% and 93%, respectively.

Discussion

The risk of cancer is increased in patients with dermatomyositis and to a lesser extent in polymyositis (1-3). How the inflammatory myopathy patients should be assessed for possible cancers is still a matter of debate (23-26). Surprisingly, the place of tumor markers assays for the search of occult malignancies in dermatomyositis and polymyositis has been poorly assessed (8, 27). We have evaluated the diagnostic values of serum tumor markers, namely CEA, CA15-3, CA19-9, and CA125, in a large cohort of patients with dermatomyositis/polymyositis. All patients had a muscle biopsy and clinical, biological, and electrophysiologic findings clearly suggestive of dermatomyositis or polymyositis. To improve our evaluation, we have excluded from our study the patients with peculiar subsets of myositis who do not carry a clear-cut increased risk of cancer. Those with childhood dermatomyositis, inclusion body myositis, and myositis associated with defined or mixed/undifferentiated connective tissue disease were excluded from the study, although recent studies suggest that they might have a slightly increased risk of tumors (3, 28). We used detailed individual charts of patients sent to our university referral center. This method provides more precise information than diagnostic coding in administrative database, which may not accurately reflect physician diagnosis as stressed recently (3). Additionally, all the cancers were diagnosed on proven pathologic grounds. Moreover, benign conditions known to elevate tumor markers, mainly CA125, were cautiously ruled out, especially pericardial or pleural effusion by echocardiogram or chest CT, respectively.

Within this selected population of 102 dermatomyositis/polymyositis patients, we have observed 10 solid cancers (9.8%). This percentage is in good accordance with that of Sigurgeirsson et al. (refs. 1, 2; 9% for polymyositis and 15% for

dermatomyositis), inasmuch as we did not take into account hematologic malignancies whose screening is poorly improved by the determination of the tumor antigens studied here. The median follow-up of our study (56 months) was close to the 5-year period of higher risk of developing cancers reported in previous studies (1-3). Six of the 10 cancers (60%) were diagnosed during the first year following screening.

We have observed that initial elevated serum levels of CA125 and/or CA19-9 are associated with a high risk of developing cancer (OR, 29.7; 95% CI, 8.2-106.6 and OR, 4.5; 95% CI, 1-18.7, respectively). CA19-9 PPV for cancer is equal to 27.3% and CA125 PPV to 62.5%. The CA125 PPV (62.5%) found in inflammatory myopathy patients may be compared, for example, with the CA125 PPV for ovarian cancer in the general population, estimated at 2.3% (10). Because the median age of women included in our study was 53 ± 15.5 years, we used a serum CA125 threshold value of 35 units/mL. In healthy postmenopausal women, this cutoff level gives a specificity of 0.98 (the probability of a negative test in the absence of ovarian cancer; ref. 29). Because serial determinations of CA125 level have been proposed to improve its usefulness for screening ovarian cancer (29-31), we have measured CA125 and CA19-9 levels 3 to 6 months after the first assessment. None of the patients without cancer had a CA125 or CA19-9 level over the threshold at the second measurement. Additionally, comparison of individual values showed that increase of CA125 from baseline to the second assessment was associated with the subsequent development of cancer. It should be emphasized, however, that this increase of CA125 was not associated with the diagnosis of ovarian cancer but also with other types of cancers. Interestingly, a 2-fold increase of CA125 was observed in one patient who further developed a peritoneal papillary cancer. The doubling of CA125 has been proposed by Zurawski et al. (30) to increase the specificity of the CA125 assay to detect ovarian cancer. Our results are consistent with those of Whitmore et al. (27) who found that CA125 was elevated in two of four dermatomyositis patients with ovarian cancer (on stored serum obtained 5 and 13 months before the date of diagnosis of cancer) and in none of the 10 controls. This study revealed that CA125 elevation was associated with an OR of ovarian cancer in dermatomyositis of 20 (95% CI, 0.64-633). However, the sample size was too small to draw firm conclusions.

Because test accuracy varies with the prevalence of malignant diseases in the studied population, we next assessed diagnostic values of screening CA19-9 and CA125 in inflammatory myopathy patients without ILD. Indeed, it has been previously suggested that in inflammatory myopathy patients the presence of ILD either alone (20) or associated with antisyntetase antibodies (21) is negatively associated with risk of cancer. Our data confirm and extend these findings because none of our patients with cancer had ILD, and there was a trend towards a negative association between the presence of ILD and of cancer. When the analysis was restricted to inflammatory myopathy patients without ILD, we found an increase of the diagnostic values of screening CA19-9 and CA125.

Our findings provides useful information to the physician diagnosing a polymyositis or dermatomyositis before scheduling a possible extensive diagnostic procedure for cancer. Our data can be summarized as follows:

- (i) CA125 and CA19-9 assessment could be useful markers of the risk of developing tumors for patients with dermatomyositis and polymyositis and should therefore be included in the search for cancer in dermatomyositis/polymyositis patients, especially for inflammatory myopathy patients without ILD.
- (ii) The risk of developing cancers is high in inflammatory myopathy patients during the first year following increased CA125 and/or CA19-9 levels.

- (iii) Raise of CA125 at serial determinations increases the risk of developing cancer.

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