Tumor markers in familial Mediterranean fever and their correlation with the frequency of attacks

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Received on January 2, 2008; accepted in revised form on July 29, 2008.

Clin Exp Rheumatol 2008; 26 (Suppl. 50): S114-S116.

Key words: Familial Mediterranean fever, tumor markers, acute phase reactants, CA 72.4.

Competing interests: none declared.

ABSTRACT

Objective. *Serum levels of tumor markers can be elevated in several benign diseases affecting the serosal surfaces. Familial Mediterranean fever (FMF) is a genetic disease characterized by acute attacks of fever and inflammation of the serosal membranes. The aim of this study was to examine the levels of tumor markers in FMF patients and their correlation with the frequency of attacks.*

Methods. *Serum levels of CA 125, CA 19-9, CA 15-3, CA 72-4, CEA, and AFP were measured by ELISA in 36 patients with a definitive diagnosis of FMF (21 males, 15 females, mean age 36.4±10.3 yrs) and in 19 healthy controls.*

Results. *Serum levels of all tumor markers were normal in the controls. In FMF patients serum levels of CA 125, CA 19.9, CA 15.3, CEA and AFP were within normal ranges, whereas CA 72.4 was significantly higher than in the controls (p=0.001). Half of the FMF patients showed increased levels of CA 72.4; the mean level was lower in those in complete remission. However, no statistically significant correlation was found between FMF attacks and acute phase reactant levels.*

Conclusion. *With the exception of Ca 72.4, serum levels of tumor markers are not affected by changes in inflammatory cytokines levels during FMF attacks.*

Introduction

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder characterized by acute attacks of fever and inflammation of the serosal membranes, including the peritoneum, pleura, and synovium (1-3). The clinical course of FMF is typically marked by exacerbations and remissions that occur in parallel to fluctuations in acute phase response proteins. Levels of some acute phase reactants, such as fibrinogen and C-reactive protein (CRP), are elevated during FMF attacks and returned to normal during attack-free periods. However, sub-clinical inflammation can persist in some FMF patients, who experience a continuous acute phase response (4).

Tumor markers are biochemical indicators of the presence of neoplastic proliferation and can be detected in the serum, plasma and other body fluids. The main utility of tumor markers is in determining the response to cancer treatment and in monitoring for recurrence during the follow-up. Nevertheless, it is a well-known fact that tumor markers may also be raised in various benign diseases, especially those involving the pleura or peritonium (5-8). Serosal inflammation is a cardinal feature of FMF; peritonitis and pleuritis occur in 93.7% and 31.4% of FMF patients, respectively (9). However, to the best of our knowledge, the effect of FMF attacks on serum levels of tumor markers has not been previously examined. This study was undertaken to investigate levels of tumor markers in FMF patients and their relationship to the frequency of attacks.

Materials and methods

Thirty-six patients with a definitive diagnosis of FMF and 19 healthy controls were enrolled. The levels of CA 125 (Immulite 2000 OM-MA, EURO/DPC Ltd, UK), CA 19-9 (Immulite 2000 GI-MA, EURO/DPC Ltd), CA 15-3 (Immulite 2000 BR-MA, EURO/DPC Ltd), CA 72-4 (RIA DE CA 72-4 Fujirebio Diagnostics, Inc, Malvern), CEA (Immulite 2000 CEA, EURO/DPC Ltd), and AFP (Immulite 2000 AFP, EURO/DPC Ltd) were measured by the ELISA method on serum samples stored at -20°C.

The normal ranges for these tumor

markers are: CA 125 (0-35 U/ml), CA 19-9 (0-39 U/ml), CA 15-3 (0-31 U/ml), CA 72-4 (0-4 U/ml), CEA (0-4.3 U/ml) AFP (0-7.02 U/ml).

Statistical analysis was carried out using the χ^2 test, the Mann-Whitney test, and Spearman's correlation.

Results

A total of 36 patients participated in the study: 21 (58%) males and 15 females with a mean age of 36.4±10.3 years. The mean age of the controls was 40.9±10.9 years and 13 (68%) were male. The FMF patients and controls were similar in age (p=0.128) and sex (p=0.800) distribution. Most of the patients (n=33, 91.7%) were on colchicine treatment: 31 (86.1%) were taking colchicine regularly and 2 (5.6%) irregularly. Amyloidosis was present in 3/26 (11.5%) patients. The attack frequency was more than one per month in 5 (14%), one or less per month in 23 (64%), and none in 8 (22%) patients. One-third (12 pts) were experiencing an FMF attack when the serum sample was collected. Levels of all tumor markers, including CA 72.4, were normal in the controls. Serum levels of CA 125, CA 19.9, CA 15.3, CEA and AFP were within normal ranges in all patients except for 2 attack-free patients who showed increased CA 125 and AFP levels of 41 U/ml and 9 U/ml, respectively.

Serum CA 72.4 was measured in 27 FMF patients and was found to be significantly increased compared to the controls (p=0.001). A total of 14 (51.9%) patients had elevated CA 72.4 levels, although this did not appear to be related to disease activity as a similar proportion of patients with quiescent disease (8/16, 50.0%) and patients in the midst of an attack (6/11, 54.5%) (p=0.816) had raised titers.

The mean CA 72.4 level was lower in patients in complete remission (3.4±0.9 U/ml) than in those experiencing an FMF attack (40.1±38.3 U/ml), but this difference was not statistically significant (p=0.075).

There was a positive correlation between fibrinogen and CRP (r=0.548, p=0.005). However, Ca 72.4 was not correlated with fibrinogen (r= -0.028, p=0.903) or with CRP (r= -0.092, p=0.701).

Discussion

The findings here suggest that serum levels of CA 19.9, CA 15.3, CEA and AFP do not change in FMF patients. Patients suffering attacks while on colchicine treatment frequently had increased serum CA 72-4 levels, although a correlation with the attacks or the acute phase response was not demonstrated by this study.

Several cytokines have been shown to be useful in the diagnosis of acute exacerbations and in the follow-up of FMF patients. Interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), soluble interleukin-2 receptor (sIL-2r), the erythrocyte sedimentation rate (ESR), and CRP all increase, especially during attacks (10). Additionally, about two-thirds of FMF patients experience continuous inflammation even when they are clinically in remission (3, 11). IL-6, IL-8, TNF-α and soluble E- and L-selectin levels are also increased in attack-free FMF patients (12). Even when ESR, CRP, fibrinogen and ferritin levels are within the normal range during attack-free periods, the serum amyloid A protein (A-SAA) level can increase up to 150 times the normal level (13). Furthermore, A-SAA dramatically decreases after increasing the colchicine dose. It has also been suggested that the changes in plasma and platelet 5-HT levels may be attributable to the role of serotonin in the inflammatory cascade of FMF (14).

Tumor markers can be elevated in diseases other than malignancy, such as kidney, liver and circulatory disturbances. Raised CA 125 has been reported in endometriosis (5) and tuberculous peritonitis (6). The serum level of CA 125 was shown to be associated with the clinical status of heart failure and its prognosis, and therefore is a potential marker of the status and clinical course of heart failure before and after heart transplantation (7). The production site of CA 125 in heart patients has been hypothesized to lie in the peritoneal mesothelium, where congestion may lead to the secretion of CA 125. The proposed explanation is that IL-6, which is elevated in heart failure, induces the proliferation of CA 125-producing cells. Contrary to the expectation that the acute phase response of IL-6 could cause an elevation, almost all the patients in our study had normal CA 125 levels.

CA 72.4 is a relatively new marker that is used for the follow-up of gastric cancer. This antibody is a high molecular weight (220-400kd) mucin-like protein that can detect tumor-associated glycoprotein (TAG) 72 (15). In the present study the mean serum level of CA 72.4 was higher in patients with frequent attacks. However, the difference was not statistically significant nor was it correlated with the acute phase response. We believe that this was due to the small sample size and large standard deviation of CA 72.4 levels in our study, since it was found during the follow-up of one patient with high serum CA 72.4 levels that these levels fluctuated with the attacks and no malignancy could be detected on screening by abdominal tomography or upper and lower gastrointestinal endoscopy. Similarly to CA 125, increased inflammatory cytokines in FMF could cause a proliferation of CA 72.4-producing cells. It may be suggested that CA 72.4 is secreted from the serosal surfaces, especially the peritoneal surface, since serosal inflammation plays a central role in the pathogenesis of FMF.

In conclusion, apart from Ca 72.4, serum levels of tumor markers were not affected by elevated inflammatory cytokines during FMF attacks. A group of FMF patients experiencing attacks while on colchicine treatment showed increased serum levels of Ca 72.4. This finding is important to avoid unnecessary tests for the diagnosis of cancer. A prospective follow-up study enrolling a large number of FMF patients is needed in order to examine the potential of Ca 72.4 as a new marker of inflammation in FMF.

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