TUMOR MARKER REQUESTS IN A GENERAL TEACHING TURKISH HOSPITAL

Gülsen Yılmaz, Fatma Meriç Yılmaz, Mehmet Senes, Dogan Yucel

Clinical Biochemistry Laboratory, Ankara Hospital, Ministry of Health, Ankara 06340, TURKEY

ABSTRACT

Serum tumor markers may be requested inappropriately by clinicians. In this retrospective study, we aimed to investigate the appropriateness of TM requests in our hospital. Patients in the study were identified from the TM requests for 3 months between June-August 2004, using the laboratory database. A total of 2249 patients (1351 men, 898 women) were included in the study and there were 6570 TM requests. The number of requests were 1050 (16%) for Carbohydrate Antigen 19-9, 993 (15.1%) for Cancer Antigen 125, 941 (14.3%) for Prostate Specific Antigen, 921 (14%) for free PSA, 925 (14.1%) for Cancer Antigen 15-3, 788 (12%) for Alphafetoprotein, 730 (11.1%) for Carcinoembryonic Antigen and 222 (3.4%) for AFP / Human Chorionic Gonadotrophin. Our findings support the idea that for the evidence-based use of TM requests the education of clinical staff is required. Clear clinical guidelines including recommendations about the appropriate use of TM can be useful for this education process. Careful audit studies are also useful to determine the impact of these guidelines on the practice of evidence-based laboratory medicine.

KEY WORDS

Evidence-based laboratory medicine, Tumor markers, Cancer, Laboratory management.

INTRODUCTION

Cancer is a significant cause of mortality and morbidity throughout the world. Early detection of cancer is essential for the best chance of cure. Serum tumor markers (TM) are widely used for cancer diagnosis, evaluation of cancer status, and monitoring treatment. TM are considered as the proteins that ideally indicate the presence of malignancy. These markers can be found in tumor cells only, or in normal cells and overexpressed in malignant cells (1). TM are associated with cancer development although slightly higher levels of TM are detected in benign disorders.

Each TM has different properties and a variable usefulness for screening, determining diagnosis, prognosis and response to therapy, monitoring the recurrence of cancer. Alphafetoprotein (AFP), the useful marker in hepatocellular carcinoma, is also found increased in benign conditions such as acute hepatitis and reflects liver cell proliferation (2).

Carcinoembryonic Antigen (CEA), an oncofetal protein, is overexpressed in adenocarcinoma, especially colorectal cancer and is also found slightly increased in benign liver failure (3,4). Cancer Antigen 125 (CA 125), a glycoprotein normally expressed in cholemic epithelium during fetal development, is associated especially with epithelial ovarian cancer, although elevated levels are found in multiple benign disorders stimulating the serosal surfaces (5,6). Cancer Antigen 15-3 (CA15-3) is the preferred TM in breast cancer. Carbohydrate Antigen 19-9 (CA19-9), an intracellular adhesion molecule, is elevated in patients with pancreatic and biliary tract cancers. Slightly increased antigen values have also been observed in cirrhosis, cholestasis, cholangitis and pancreatitis (7). The beta subunit of human chorionic gonadotrophin (β -HCG) is normally produced by placenta, elevated levels are found in pregnancy, germ cell tumors and gestational trophoblastic diseases (8). Prostate-Specific Antigen (PSA) is a glycoprotein that can rise in prostate cancer, prostatitis, benign prostate hypertrophy, prostatic trauma and after ejaculation, and is produced by the prostatic epithelium (9).

Address for Correspondence :

Dr. Dogan Yucel
Clinical Biochemistry Laboratory, Ankara Hospital,
Ministry of Health, Ankara 06340, TURKEY
E-mail : doyuucel@yahoo.com

As mentioned above, there are many reasons besides the presence of malignancy, which causes increased levels of TM. However, TM requests are increased in most hospitals due to wider availability of TM tests on automated immunoassay systems and decreased turn around time of the assays. These

relatively expensive tests may be inappropriately requested by clinicians. Although a few guidelines exist for TM use, there is a necessity of an audit in the use of TM in general practice according to the principles of evidence-based laboratory medicine. In this retrospective study, we aimed to investigate the appropriateness of TM requests in our hospital as an overburdened teaching hospital.

METHODS

Patients in the study were identified from the TM requests for 3 months between June-August 2004, using the laboratory database. Hospital information system, from where we got the information for the diagnosis, biopsy results, treatment and required information about the patients was available from June 2004 in our hospital. 3-month investigation was preferred in order to go into details about the patients. The patient demographics like age and sex; the diagnosis of the patients and the results of other tests and biopsies were obtained from the hospital information system. The TM requests at the same time period in 2003 were also gathered in order to evaluate the changes in the workload. The preference of the same time period was to eliminate the effect of time between the years. The study was approved by Local Ethics Committee of our hospital.

TM requests were classified in three categories: a) screening, b) diagnosis of a cancer and c) detecting the recurrence or metastasis of a cancer. Screening purposes except PSA requests were considered as inappropriate use. The patients who had biopsies related with the requested TM were recorded and the results of the pathological diagnoses were classified as benign or malign diseases. AFP, CEA, CA125, CA 19-9, CA 15-3 and β HCG analyses were made on an E 170 immunoassay analyzer (Roche Diagnostics). Internal and

external quality assessment were achieved during the study period. Reference intervals of the TM studied are shown in Table 1. All of the statistical analyses were made by using Microsoft Excel.

RESULTS

A total of 2249 patients (1351 men, 898 women) were included in the study and there were 6570 TM requests. The mean age was 51.6 ± 7.07 (54.9 ± 20.5 for men, 45.9 ± 14.8 for women). The number of requests were 1050 (16%) for CA 19-9, 993 (15,1%) for CA 125, 941 (14,3%) for PSA, 921 (14%) for fPSA, 925 (14,1%) for CA 15-3, 788 (12%) for AFP, 730 (11,1%) for CEA and 222 (3,4%) for AFP/ β HCG. The most commonly ordered test was CA 19-9 (16%). CA 125 and PSA were the other commonly requested tests (15,1% and 14,3%, respectively). The departments of urology (24%) and general surgery (16%) have made the most TM requests of total including and excluding PSA requests (Figure 1).

A total of 2949 TM requests had done in 2003 between 01/06-31/08. The number of requests at the same time period in 2004 was 6570. The distribution of the ordered TM according to the years is shown in Figure 2. The major increase was in CA 19.9 and PSA requests.

An evaluation was made for each TM by grouping the tests in three categories as mentioned above. The most common reason for AFP requests was screening of the hepatitis or cirrhosis patients. CA 125 orders were made frequently from the postmenopausal women. The classification of the TM according to the categories are shown in Table 2.

Figure 1. Distribution of TM orders between departments (Including PSA requests).

Table 1 : Reference intervals of the tumor markers.

Tumor Marker	Reference Interval
AFP (μ g/L)	0-7
CA 125 (kU/L)	0-35
CA 15-3 (kU/L)	0-25
CA 19-9 (kU/L)	0-34
CEA (μ g/L) smokers	0-4.3
CEA Non-smokers (μ g/L)	0-3.4
PSA (μ g/L)	0-4
free PSA (μ g/L)	0-1
β HCG (U/L) non pregnant women	0-5,3
β HCG (U/L) men	0-2,5

Figure 2. Distribution of TM requests according to the years.

The evaluation was made including and excluding PSA and fPSA requests separately: 941 requests were done for PSA, 150 patients had elevated PSA levels and 98 biopsies were performed. Total number of patients who had pathological

Table 2 : Classification of TM requests according to the reason of order. a) screening, b) diagnosis of a cancer, c) detecting the recurrence or metastasis of a cancer

	a	b	c
AFP (hepatocellular cancer)	762	14	12
CA 125 (ovarian cancer)	902	75	16
CA 15-3 (breast cancer)	879	39	7
CA 19-9 (pancreatic or biliary tract cancers)	1014	29	7
CEA (colorectal cancer)	660	45	25
AFP/βHCG (germ cell tumors)	203	16	3

prostate cancer diagnosis were 7; which 5 of them had elevated and 2 had "normal" PSA levels.

Excluding PSA requests; a total of 37 patients had a cancer diagnosis pathologically. Of them, 25 had elevated, 12 had normal TM levels, and 261 patients had increased TM levels but had no biopsies or benign pathological diagnosis (Figure 2).

Two hundred and twenty-seven of 993 requests for CA 125 and 246 of 925 CA 15-3 requests were made for male subjects; 8 orders for PSA were made from female subjects without any pathology.

DISCUSSION

TM requests become more and more excessive in recent years. The great number of TM requests shows that there is a

necessitate of an audit for the use of TM in spite of a few guidelines for TM were published (10,11). Our hospital does not include an oncology department so the TM use in this study reflects the general practice.

The results of this study showed that there is an increased workload in the tumor marker requests. While there was a 123% increase in the total number of TM requests, only 8.3% increase in the total test number was determined between 2003 and 2004 at the same time period. In respect of the number of cancer diagnosis in 2004, a great difference between TM requests and cancer diagnosis were considered. This finding supports being more aware of appropriate TM testing and making orders more comfortable.

Our findings suggest that most of TM are used for screening and as a part of diagnostic strategy by clinicians in our hospital. The most critical problem in orders was requesting all TM instead of one or maximum two appropriate requests. It may be proved by the number of CA 125 and CA 15-3 orders in men. Twenty-three percent of CA 125 (a marker of ovarian cancer) and 26,6% of CA 15-3 (no breast cancer diagnosis or suspicion in men) requests were made for male subjects while only 8 orders (0,01%) for PSA and fPSA were made for female subjects. If this misuse resulted from simple personal mistakes, the percentages of errors in each TM must be equal or similar. However, the gender error in CA 125 and CA 15-3 requests was fairly more than PSA and fPSA requests. In a recent study, 17% and 26% of CA 125 and CA 15-3 requests made for men respectively (12) and these percentages were similar with our study. The number of tests performed on the wrong sex of patients showed the necessity for giving more information regarding the use of these markers. Even clinicians ordered such a TM request, the laboratory could reject these tests before the analyses. Thus, cost effectiveness of TM can be provided by the laboratory itself.

Most of TM requests were CEA, CA 19-9 and CA 125 that ordered for gastrointestinal tumor suspicion. However, in gastrointestinal tumors multiple TM requests have no superiority to single TM request and do not exactly improve the sensitivity or specificity of individual markers (13,14). There can be differences between recommendations about which markers should be measured in specific malignancies. For example The Standards, Options and Recommendations (SOR) recommends that in the absence of raised CA 125 levels at presentation for ovarian cancer, CEA and CA 19-9 can be measured additionally (10).

Screening for malignancy did not help to determine the source

of the primary tumour because the site was known in most cases while ordering TM, e.g. screening ovarian cysts, screening hepatocellular carcinoma in hepatitis patients, screening for benign prostate hypertrophy. On the other hand, the percentage of biopsies in patients who have elevated levels of TM was higher than the percentage of biopsies in patients with normal TM levels (Figure 3). Also the proportion of cancer diagnoses was significantly higher in patients with elevated TM levels. Elevated TM levels was a warning and clinicians required further researches for these patients especially pathological side.

Most of TM requests were made from urology department and the most popular tests were PSA and fPSA as expected. When PSA and fPSA were excluded, general surgery department made maximum TM orders. On the other hand infectious disease department had the most number of patients. The increase in TM requests for general surgery was resulted from ordering TM altogether although only one or two TM requests were used appropriately.

The data is evaluated in the name of patients and tests separately. The number of requests were 2.95 (1-7) for each patient. The most ordered test was CA 19-9 (16%). It was mostly requested for screening pancreatic cancer and gastrointestinal cancers. CA 125 and PSA were the other commonly requested tests (15,1%, %14,3). CA 125 can be used to screen women with a strong family history of ovarian cancer (15). AFP and CEA were the other most popular requested tests in our hospital (12%, 11%). AFP orders was generally made in patients with hepatitis by infectious disease department. The percentage of each of TM requests was similar. As mentioned above, it may be caused from ordering all of the TM instead of one or two appropriate TM requests.

In conclusion this study showed the significant rise of TM requests even though it is a retrospective study for 3 months-period. Despite published guidelines, screening is still the main purpose of TM orders and may cause unnecessary worries and increasing cost. In our laboratory increasing cost of TM is a growing problem. The total amount of money paid for TM is \$6300 in 2003 and \$13050 in 2004. These findings support the idea that for the evidence-based use of TM requests the education of clinical staff should be put into the practice. Clear clinical guidelines including recommendations about the appropriate use of TM can be useful for this education process. Careful audit studies are also useful to determine the impact of these guidelines on the practice of evidence-based laboratory medicine. At the same time, training of laboratory staff must be carried out, so by preventing mistakes (e.g. orders

Figure 3. The proportions of pathological diagnoses and biopsies in the patients who have A. elevated, B. "normal" TM levels.

in wrong sex of patient) and the laboratory itself must contribute to cost effectiveness of TM.

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