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# Tumor markers in screening for neoplasms in patients with idiopathic deep vein thrombosis

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## Abstract

The aim of this study was to evaluate the CEA, CA 125, CA 15-3, CA 19-9 and AFP tumor markers as screening tests for neoplasms in idiopathic deep venous thrombosis (DVT). The hospital records of 500 patients with confirmed diagnosis of DVT by lower limb Doppler ultrasonography were assessed in retrospective longitudinal and quantitative study in Hospital de Base Medicine School, São José do Rio Preto in the period from January 2005 to March 2010. An investigation of tumor markers had been randomly requested for 167 of these patients. There was significant difference for the CEA marker in patients with neoplasms detected after idiopathic DVT (124.42 ± 474.82) compared to other patients in this group (1.64 ± 1.41; p = 0.0017, 95% confidence interval (CI): -198.76 to -46.788) and for the CA 15-3 marker (57.5 ± 0.707 in patients with cancer and DVT and 18 ± 11.015 in patients with only idiopathic DVT; p = 0.0019; 95% CI: -58.844 to -20.156). Only the CA 15-3 marker proved to be noticeably sensitive for screening in the statistical tests. Cancer was diagnosed in 32% of 28 the patients who had elevated levels of at least one of the markers. All patients without diagnosis of malignancy had serum levels of tumor markers within the reference values. An investigation of tumor markers proved useful both in the exclusion of malignancies and to indicate screening utilizing other more specific examinations for patients with a high probability of neoplastic syndrome.

**Key words:** Deep venous thrombosis, screening program, cancer, paraneoplastic syndrome

## Introduction

Deep vein thrombosis (DVT) is a common manifestation in patients with cancer and may appear as the first manifestation of a disease [1,2]. Malignant neoplasms are responsible for a 20% increase in the incidence of thromboembolic events [3]. Patients with Deep Vein Thrombosis (DVT) have an incidence of idiopathic cancer of between 4.6% and 25%. This justifies the investigation of underlying malignant disorders in these patients [4-6]. On considering all patients with cancer, those with DVT have a significant reduction in survival rates with a four- to eight-fold higher risk of death [7].

According to the literature, early diagnoses of occult neoplasms after acute episodes of DVT are reached in 61% of patients submitted to screening compared to only 14% for those who chose an outpatient follow-up [5]. Tumor markers are macromolecules present in the tumor, blood or in other biological fluids; changes in concentrations are related to the genesis and growth of neoplastic cells. Among the main tumor markers are alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), CA 125, CA 15-3 and CA 19-9[8]. In adulthood, normal serum levels of these biomarkers are as follows: AFP between 5 ng/mL and 15 ng/mL, CA 125 = 35 U/mL, CA 19-9 = 37

U/mL, CA 15-3 = 25 U/mL and CEA = 3.5 ng/mL in nonsmokers and 7 ng/mL in smokers [7].

The aim of this study was to evaluate the CEA, CA 125, CA 15-3, CA 19-9 and AFP tumor markers as screening tests for cancer in patients with idiopathic DVT.

## Method

The hospital records of 500 patients with diagnosis of DVT confirmed by lower limb Doppler ultrasonography were assessed in a retrospective longitudinal and quantitative study in Hospital de Base Medicine School, São José do Rio Preto in the period from January 2005 to March 2010. Patients were enrolled in this study if measurement of serum levels of the CEA, CA 125, CA 15-3, CA 19-9 and AFP tumor markers had been requested during hospitalization to screen for underlying malignancies. The criteria used to request the measurement of these serum levels were not stated in any of the patients' records. The following cutoff values were suggested by the manufacturers of the tests: 3.5 ng/mL, 35 U/mL, 25 U/mL, 37 U/mL and 15 ng/mL for CEA, CA 125, CA 15-3, CA 19-9 and AFP, respectively. Subjects with risk factors for DVT (such as major surgery, bed rest, women using hormone therapy or postpartum) and those with prior diagnosis of cancer or previous acute DVT were excluded from the study. This study was approved by the Research Ethics Committee of the Medicine School in Sao Jose do Rio Preto.

The data were analyzed by descriptive statistics specific to each variable as well as univariate analysis using the chi-square test, the Fisher exact test and the t-test. An alpha error of 5% (p-value < 0.05) was considered acceptable.

## Results

Data on age and gender are shown in the Table 1. A total of 145 participants had positive serum levels of AFP, with occult neoplasia being diagnosed in 11 (7.5%) of these cases using other diagnostic methods and confirmed by histopathological analysis. The mean serum level of the AFP tumor marker found in this group was 3.54 ± 2.40 whereas in those with only idiopathic DVT without evidence of underlying malignancies the mean serum level was 3.77 ± 3.37 (p = 0.825; 95% confidence interval: -2.286 to 1.826).

On reviewing the patients' charts, the serum CA 125 level was positive for 68 patients. The mean level was 22.67 ± 13.66 for the 6 (8.8%) patients who presented with occult neoplasms and 33.76 ± 91.80 (p = 0.769, confidence interval 95% to 86.499 -64.317) in the group for whom screening found no signs of malignancy.

Table 1: Patients with idiopathic DVT according to gender and mean age

| | N | | | | | Mean age | | | |
|---|---|---|---|---|---|---|---|---|---|
| | iDVT+ CA | | iDVT | | Total | iDVT+ CA | iDVT | se | sp |
| | M | F | M | F | | | | | |
| CA 15-3 | 1 | 1 | 5 | 2 | 9 | 71 | 60.14 | 100% | 87.5% |
| CEA | 9 | 6 | 65 | 79 | 159 | 66.33 | 58.73 | 6.67% | 91.14% |
| CA19-9 | 7 | 4 | 54 | 59 | 124 | 65.45 | 60.14 | 9.09% | 95.58% |
| CA 125 | 5 | 0 | 47 | 15 | 67 | 60.17 | 63.16 | 50% | 91.94% |
| AFP | 6 | 5 | 62 | 72 | 145 | 65.2 | 59.88 | 0 | 96.77% |

M: men; F: women; iTVP: idiopathic deep venous thrombosis only; iTVP + CA: idiopathic deep venous thrombosis and diagnosis of occult neoplasia; se: Sensitivity; sp: Specificity

It was observed in this study that 22.2% of individuals with idiopathic DVT who were later diagnosed with cancer had a mean serum level for CA 15-3 of 57.5 ± 0.707 U/mL and for 7 subjects where the diagnosis of DVT remained idiopathic the mean level was 18 ± 11.015 U/mL (p = 0.0019, 95% confidence interval: -58.844 to -20.156). Besides identifying significantly higher serum levels of tumor markers in patients where cancer was later diagnosed, the diagnostic test proved highly sensitivity (100%) with a positive predictive value of 66.67% (95% confidence interval: 0.094299 to 0.991596). The specificity was also significantly high (87.5%) with a negative predictive value of 100%.

In this study, biomarker tests, including for CEA, were performed for 159 patients. Of these, 9.4% had malignant tumors preceded by idiopathic DVT with a mean serum CEA level of 124.42 ± 474.82. For the other patients in this group the estimated mean level of CEA was 1.64 ± 1.41 (p = 0.0017, 95% confidence interval: -198.76 to -46.788). Although serum CEA levels are significantly increased in patients with occult neoplasms, the sensitivity of this marker was only 6.67% (95% confidence interval: 0.001686 to 0.319485) and the positive predictive value was 8.86%. The specificity of the test is high (100%) with a negative predictive value of 91.14%. In this study, we found increased levels of this marker in two patients with colorectal cancer, one with kidney cancer and one with metastatic carcinoma of undetermined site.

The serum CA 19-9 levels in subjects with underlying malignancies (11 patients) and where participants were not diagnosed with malignant disease (91.29%) were 17.183 ± 12.205 and 12.451 ± 14.590, respectively (p = 0.3; 95% confidence interval: -13.740 to 1.279). The sensitivity of the test was not significant (9.09%) with a positive predictive value of 16.67% however the specificity was high (95.58%) with a negative predictive value of 91.53%.

The sensitivity of the test for CA 125 was intermediate (50%) with a positive predictive value of 28.57%, high specificity (91.94%) and negative predictive value of 96.91%. Two patients (33%) with undiagnosed cancer had higher values than the reference values for CA 125. Two other patients (16.7%) had malignant tumors and AFP higher than the reference values. For these latter two markers, there were no significant differences between the serum levels of patients with occult neoplasms and those without malignant disease.

All patients that did not have future diagnoses of malignancies presented with tumor marker serum levels within the reference values.

## Discussion

This study identifies an association between tumor markers in patients with idiopathic DVT and occult malignancies. The mean age of patients with cancer (66.33 years) was statistically similar to the mean age calculated for patients without underlying neoplasms (58.95 years; p-value = 0.7). A study in the same service identified different prevalences in cancer between 50 to 60-year patients (16.6%) and 60 to 70-year patients (26.8%) suggesting that although the mean age was not significant, the risk for neoplasms at aged 60-70 years is higher. The prevalence dropped to 19.3% for the 70 to 80-year age group 1. This data illustrates the need for systematic screening particularly in the 60 to 70-year age group.

The results showed that there were significant differences in the levels of CEA (p = 0.0017) and CA 15-3 (p = 0.0019) between patients with occult malignancies and those where no evidence of malignancy was detected. However, only CA 15-3 proved to be sufficiently sensitive in statistical tests for screening, even with the small number of individuals in this sample. Thus, the association of CA 15-3 in patients with cancer after acute thrombotic events should be confirmed in future studies. We found no studies indexed to the Pubmed, Scopus and ISI medical databases that explored this association.

It is well known that CA 15-3 is a tumor marker for breast cancer, as well as for ovarian, lung, cervix, and liver cancer and for lymphomas [8]. Due to its low specificity in studies of the general population, it is not indicated as a diagnostic method [8]. In patients with idiopathic DVT however, the marker appears to be a useful method when neoplasms are suspected. The necessity of investigations is justified as, when the diagnosis of malignancy is made in the early stages of the disease due to early screening for cancer in patients with idiopathic DVT, the therapeutic response is better and life expectancy is increased [9].

There is a study that reported that an evaluation of the set of cancer markers, CEA, AFP and CA 125, was positive in 27 of a group of 99 patients with idiopathic DVT; approximately 25% of them were diagnosed with cancer. In addition, 49 patients presented with at least one positive marker, with 16.3% of these being diagnosed with cancer [9]. In this study, 28 patients had at least one marker higher than the reference range; about 32% of these were diagnosed with cancer. The absence of abnormal results in the levels of the markers of some patients seems to be related to the absence of occult malignancies. Thus, the CEA, CA 125, CA 15-3, CA 19-9 markers were useful in excluding malignancies; patients with positive results should be referred for other tests such as endoscopy, chest x-ray, abdomen ultrasound and colonoscopy.

The present study suggests that tumor markers, particularly CA 15-3, may be used to identify the possibility of underlying cancer in patients suffering from acute thrombotic events such as idiopathic DVT. This technique should not be used alone but combined with more accurate evaluation methods. Besides the investigation of paraneoplastic syndrome, investigations of other possible causes of hypercoagulability are suggested [10-11].

## Conclusion

An investigation of tumor markers proved useful both in the exclusion of malignancies and to indicate screening utilizing other more specific examinations for patients with a high probability of neoplastic syndrome.

## Conflict of Interest

The authors certify that stud not have of Conflicts of Interest and agree with the content of the manuscript.

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