Screening for Cancer in Patients with Idiopathic Venous Thromboembolism: The Clinical Practice

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Key Words

Thromboembolism, idiopathic venous • Cancer

Abstract

The reported incidence of concomitant cancer in patients with idiopathic venous thromboembolism (IVTE) varies between 4 and 24%, while the mean incidence of cancer within 3 years thereafter approximates 9%. Baseline investigations of patients with IVTE have been recommended. We evaluated the clinical practice regarding the screening of these patients according to these recommendations in two teaching hospitals. Medical history and physical examination were done reasonably exhaustively, except for investigations of the urogenital tract. Laboratory and imaging investigations were performed incompletely in a substantial proportion of the patients. The clinical evaluation regarding cancer, performed in patients with IVTE, could be improved. The implementation of a protocol should be considered.

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Introduction

Since the initial observation by Trousseau [1] in 1865, the association between cancer and venous thromboembolism (VTE) has been well documented. At the time of diagnosis of a first episode of VTE, approximately 15% of the patients have an active malignancy [2–4]. In those with idiopathic, i.e. unexplained VTE (IVTE) the reported prevalence of concomitant cancer at the time of VTE varies from 4 to 24% [3, 5–13]. The difference in these figures can, to a large extent, be explained by the extensiveness of the investigations performed at presentation. The mean incidence of cancer within 3 years after an episode of IVTE in patients older than 40 years, who did not have overt cancer at the time of VTE, is 9% (reported range 3–26%). Most of these cancers will become clinically apparent within the first 6 months [3, 5–7, 11–18]. Screening these patients for their still occult cancer could theoretically lead to early intervention and might potentially improve their outcome. Consensus does not exist about the precise diagnostic workup, in particular for the initial clinical evaluation. But data of several recent studies support the concept that the evaluation of patients with IVTE should include a thorough medical history,

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physical examination, some laboratory investigations, including blood count, liver enzymes, urinalysis, feces for occult blood tests and a chest X-ray [9, 12, 16, 19–21]. Additional testing should be guided by abnormalities detected by these investigations.

Since the report of Prandoni et al. [5] our hospitals advocated a general policy regarding the evaluation of patients with IVTE, and introduced guidelines based on the published recommendations. In the present study we evaluated whether the clinical practice regarding screening for cancer of patients with IVTE was performed according to our guidelines in these two large teaching hospitals.

Methods

The inpatient registries of the Slotervaart Hospital and Academic Medical Center, both in Amsterdam, The Netherlands, were checked for the records of patients admitted for acute VTE between 1994 and 1998. Charts of patients with a known risk factor for VTE were excluded (for definitions see table 1). At random the files of 50 patients with so-called IVTE were selected in each hospital. The charts contain standardized forms, with questions regarding the medical history and physical examination. Medical students fill in the charts and they are corrected by residents in internal medicine supervised by an internist.

Data Collection

The records were checked separately by two trained investigators, by means of an a priori designed list of 20 items, and based on the recommendations for early cancer detection [9, 12, 16, 19–21]. They specifically looked for indications that the attending physicians had actively searched for signs of cancer. These signs included questions about change in bowel habits, loss of appetite, unexplained weight loss, changes in aspect or pattern of micturition, unusual vaginal blood loss and persistent cough. The investigators also checked whether the physical examination was directed towards the detection of lymphadenopathy and abnormal masses in mammae, abdomen, rectum or genitourinary tract. Furthermore, the performance and results of laboratory and radiological investigations were reviewed. The laboratory investigations were focused on blood count, liver enzymes, protein electrophoresis (to detect multiple myeloma), feces for occult blood tests and urinalysis (to detect microscopic hematuria). Using the checklist the occurrence of the various items was scored for each patients. They were only considered to have been obtained when it was specifically noted in the records. If additional screening procedures were performed, the reason for the procedure was determined. If the routine screening procedures showed abnormalities, the records were checked for additional investigations.

Besides the usual clinical practice we were interested in whether or not the attending physician explicitly mentioned a possible relationship between IVTE and cancer, while performing the investigations. This was assessed by checking both the charts and subsequent correspondence.

Table 1. Known risk factors for VTE

Known/overt malignancy
Recent surgery (<3 months)
Recent trauma
Pregnancy
Prolonged immobilization
Lupus anticoagulans
Anticardiolipin antibodies
Factor V or factor II mutation
Hyperhomocysteinemia
(Change of) oral contraception
Deficiency of
Antithrombin III
Protein S
Protein C

Results

The mean age of the 100 study patients was 62 years (range 20–100 years); 55 were women. There were no significant differences between the findings in the two hospitals; hence the results were pooled. The results of the various items scored for the medical history, physical examination, laboratory and radiological investigations are detailed in table 2.

The medical history was obtained reasonably well, but only half of the women had been asked about unusual vaginal blood loss. In most patients the physical examination was nearly complete, with the exception of examination of the breasts, which was only performed in two thirds of the patients, and digital examinations of the rectum and vagina, which was done in 35 and 20%, respectively.

Nearly all patients had a complete blood count done. Testing of liver enzymes (37%), protein electrophoresis (60%), feces for occult blood tests (76%), urinalysis (56%) as well as chest X-ray (43%) were not performed in a substantial part of the study population.

In 15 patients the routine investigations revealed an abnormality possibly related to cancer, such as unexplained weight loss, change in bowel habits, suspect rectal, vaginal and breast examination, and anemia. Additional tests were performed in 8 of these patients and led to the diagnosis of cancer in 3 of them. One had metastasized prostate cancer, one had a renal mass of more than 10 cm and refused further evaluation and the other one had a stage I breast cancer and still is in good condition after adequate surgery. In the other 7 patients an abnormal result in the initial evaluation was not further analyzed. In

Table 2. Results of items scored for medical history, physical examination, laboratory and radiological investigations in 100 patients with IVTE

	Recorded, %
<i>Medical history</i>	
Weight loss	88
Change in bowel habits	90
Change in micturition habits	90
Unusual vaginal blood loss	51
Persistent cough	91
Loss of appetite	93
<i>Physical examination</i>	
General impression	90
Lymphadenopathy	88
Mammae	71
Chest auscultation	90
Abdomen	90
Liver/spleen	90
Digital rectal examination	36
Digital vaginal examination	22
<i>Laboratory</i>	
Complete blood count	94
Liver enzymes	63
Protein electrophoresis	40
Feces occult blood	24
Urinalysis	44
<i>Radiology</i>	
Chest X-ray	57

1 patient her mental condition (dementia) was the reason to withhold further tests, while the other 6 patients refused further evaluation because of old age and physical condition. These patients were all lost to follow-up. Although routine evaluation did not show abnormalities, additional testing was performed in 11 patients. The additional tests involved ultrasound of the abdomen in 10 patients, CT abdomen in 5, mammography in 4 and gastroscopy in 1 patients. None of these additional tests revealed signs of malignant disease.

The subjective review of the records revealed 52 cases, in which the attending physician clearly had the relation between IVTE and cancer in mind, while performing the investigations. In 12 records it was not possible to determine whether or not the relation between IVTE and cancer was actively pursued. In the remaining 36 cases there was no indication that the physicians made the association between the IVTE and (occult) cancer.

Discussion

We evaluated the current practice of screening for the presence of occult cancer in patients with IVTE in two large Dutch teaching hospitals. From a cohort of 654 consecutive patients the charts of 100 patients with IVTE were identified at random. This method, therefore, gives a representative picture of the screening procedure in patients with IVTE admitted in these hospitals during the study period.

The present investigation has some limitations. Its retrospective nature obviously might have influenced our results. On the other hand, a prospective design could have influenced the results as well. Furthermore, we relied on the charts and charts written by physicians are known to be concise. In our hospital, however, medical students completed the standardized charts in cooperation with residents. Therefore, we believe the information needed could be retrieved from the charts.

Our main findings indicate that medical history was taken and physical examination performed reasonably exhaustively. The only exceptions were questions about unusual vaginal blood loss, and examination of mammae, vagina and rectum. Additional laboratory and imaging investigations were not completed as recommended in a substantial part of the patients. The only positive exception was the performance of the complete blood count. Protein electrophoresis, urinalysis and particularly feces occult blood tests were performed in a minority of the patients. The gaps in the medical history and the physical examination might be related to the attitude of the physicians and patients towards investigations of the genital tract.

The lack of awareness of the association between IVTE and cancer is the most likely explanation for the absence of laboratory investigations and chest X-rays. This presumed lack of awareness is supported by the subjective review of the records. In as much as 36 records we could not identify any sign of the physician actively making the association between IVTE and a possible malignancy.

The recommended screening at presentation, also represented in our 20-item checklist, is not based on any study comparing survival benefit of screening with no screening in patients with IVTE. Therefore, no standard protocol exists.

However, a protocol for screening is justified when (1) the disease of interest is serious and common, (2) the natural history of the disease is well understood, (3) the screening tests applied are accurate and reliable and (4) an acceptable treatment is available [22–24]. Cancer is a seri-

ous disease and common in IVTE patients. Without treatment cancer will ultimately lead to death, the time period depending on the type and the extent of the tumor. The accuracy and reliability of routine evaluation in this setting have to be determined. For several kinds of malignancies treatment is available and could favorably influence outcome, even when the tumor is advanced (such as breast, cervix, ovary, testis and lymphoma). Even though there is no proof that the recommended evaluation has an advantage in terms of survival, there is a general consensus that the routine evaluation should be performed in patients with IVTE, because of the possible early detection of cancer [21]. The procedure mentioned is very simple, cheap and minimally invasive, with no risk for complications.

At present more extensive screening procedures are not recommended for various reasons. Recent studies could not detect a survival benefit in patients with IVTE

who underwent extensive screening involving, for example, testing of tumor markers, abdominopelvic ultrasound and computer tomography [3, 6, 9, 13]. However, most of these studies were retrospective and/or included too few patients to be able to detect a significant difference. Moreover, the costs of more extensive screening procedures are not negligible when they have to be performed in all patients with IVTE. In 10% of our population additional procedures were performed for no obvious reason. Most of the additional tests were noninvasive. They did not reveal a malignancy in any of the patients.

Our study shows that the clinical evaluation regarding cancer performed in patients with IVTE in two teaching hospitals in Amsterdam could be improved. One way is to increase the awareness of the relation between IVTE and concomitant cancer and (occult) cancer. Another possibility is to institute the recommendations more formally.

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