Idiopathic venous thromboembolism or occult cancer?

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ABSTRACT

The relationship between cancer and an increased incidence of venous thromboembolism (VTE) is well documented. VTE is a common complication of cancer, which usually occurs in the advanced stages of the disease. It often manifests itself before the cancer has been diagnosed and frequently is the first symptom of malignancy. In particular, pulmonary embolism is a major epidemiological problem because of its prevalence and high mortality. This article contains a review of the literature on VTE and occult cancer. It indicates the problem of a lack of an effective diagnostic strategy for malignancy in patients with idiopathic venous thromboembolism.

KEY WORDS: venous thromboembolism, pulmonary embolism, screening for occult cancer

INTRODUCTION

The relationship between cancer and an increased incidence of venous thromboembolism (VTE) is well documented. VTE is a common complication of cancer [1, 2]. In some patients with apparently idiopathic VTE it is actually the first symptom of undiagnosed malignancy.

EPIDEMIOLOGY

Pulmonary embolism remains an important epidemiological problem due to its incidence and high mortality. Based on a French register analysis, carried out on a population of 342 thousand residents of Brittany, the incidence of venous thromboembolism has been estimated as 183 cases/100 thousand residents/year, and that of pulmonary embolism as 60 cases/100 thousand residents/year [3]. Extrapolating from the above mentioned data to the Polish population (results of the 2011 National Census demonstrated that as of 31 March 2011 the population of Poland was 38 511.8 thousand people), around 23 thousand new episodes of pulmonary embolism can be expected each year. When it comes to mortality in pulmonary embolism, it is estimated as 7–11% [4], based on an analysis of prospective cohort trials. Translating the data again into the Polish reality, pulmonary embolism mortality in our country can be estimated as around 1600–2500 deaths annually.

Pulmonary embolism may occur in patients without any identified risk factors (idiopathic pulmonary embolism) or is provoked by one or more predisposing factors. On the basis of literature data, the percentage of patients suffering from idiopathic pulmonary embolism fluctuates between 15 and 50%. Taking into account the ZATPOL registry data on VTE predisposing factors, idiopathic pulmonary embolism has been diagnosed in 14.7% of the cases [5]. A similar percentage of patients (around 20%), without the confirmed presence of factors predisposing to venous thromboembolism, has been reported by the International Cooperative Pulmonary Embolism Registry (ICOPER) analysis [6], as well as an analysis carried out by Heit and collaborators in Minnesota, United States [7]. However, there are also results of other trials and registers at our disposal, where the percentage of patients with idiopathic venous thromboembolism amounts to as much as 50%. In the study carried out by Cushman and collaborators, 47% of the 304 study subjects were diagnosed with the idiopathic VTE [8], and a similar percentage of patients were indicated in a trial assessing the population of California, USA [9]. In an analysis of data from a prospective clinical trial on patients with deep vein thrombosis, comparing treatment efficacy of unfractionated heparin versus low molecular weight heparin, the proportion of patients with idiopathic disease was 35% [10]. The population of patients suffering from venous thromboembolism is not homogenous in terms of the manifestation of risk factors, which in turn translates into different mortality rates. Hence, in one of the studies, 28-day mortality totalled 9.4% after the first episode of deep vein thrombosis, and 15.1% after an episode of pulmonary embolism. Analysing the different subgroups of patients in the study, 28-day mortality of idiopathic VTE patients was 5.2%, while it was 7.3% in the cohort of patients with identified risk factors (secondary VTE), and as much as 25.4% in the group of patients with malignancies [8].

In around 7–10% of patients with idiopathic VTE, oncological disease is diagnosed within 1–2 years following the occurrence of a thrombotic episode or pulmonary embolism event [11–16]. The risk of proliferative disease is significantly higher in that group of patients as compared with the secondary VTE (involving the risk factors) patients or with the general population without VTE susceptibility [11, 12, 15, 19]. Additionally, the risk of cancer is substantially increased in those patients who are subject to recurrent VTE episodes [12].

In one of the studies (the Scottish registry), a substantially elevated risk of cancer development continued for 2 years after the diagnosis of venous thromboembolism, and it applied to ovarian cancer and lymphoma in particular [12]. On the other hand, in a paper by Sorenson and collaborators, the authors demonstrated in a retrospective analysis that idiopathic deep vein thrombosis or pulmonary embolism (compared with the population of subjects with no history of VTE) is associated with an increased cancer risk, including pancreatic, ovarian, hepatic (hepatocellular carcinoma), and cerebral neoplasms in particular [14]. In another study involving a group of 400 deep vein thrombosis patients, cancer was diagnosed in 13 of them within the space of 6 months from a thrombotic episode. 10 of them (77%) had idiopathic deep vein thrombosis. The prevailing neoplasms were once again those affecting the gastrointestinal tract and the urinary and reproductive system. Similar conclusions have been reached by a meta-analysis demonstrating that a sustained episode of VTE (both idiopathic and secondary) is associated with a significantly elevated risk of occult cancer, including pancreatic, ovarian, and hepatic cancers in particular.

Authors of the Swedish registry have also confirmed a 4-fold higher risk of neoplastic disease in the group of patients suffering from venous thromboembolism, and apart from the previously mentioned hepatic, pancreatic, ovarian, and cerebral cancers, they have additionally observed a higher risk of Hodgkin lymphoma and true polycythaemia. Interestingly, venous thromboembolism has been shown to increase the risk of cancer by 30% in

a long-term perspective, i.e. within the period of 10 years from a sustained VTE episode [17].

IN SEARCH OF OCCULT CANCER

It goes without saying that early diagnosis of an unadvanced cancer should lead to improved treatment efficacy, and lengthen the expected survival. In a patient after an episode of idiopathic VTE, one should carefully consider the indications for further testing for neoplasia. Some cancers can be detected with simple methods during a VTE episode, other would require a comprehensive diagnostic screening. The most frequently presented arguments against the extension of diagnostics to include highly specialist examinations are the following: high cost incurred, increased risk of complications (contrasting agent, ionizing radiation, invasive procedures), and lack of evidence coming from prospective trials in support of a beneficial impact of such an algorithm on patient survival [18].

Monreal and collaborators demonstrated in a prospective cohort study that in doubtful situations even a limited panel of tests which can be performed in an outpatient setting, such as the physical examination (including mammary gland and *per rectum* examinations), blood count, erythrocyte sedimentation rate, basic biochemical tests, determining kidney and liver functions, chest X-ray, and abdominal ultrasound, with the additional tomocomputer and endoscopic examinations, as well as selected tumour markers, increased the detectability of occult cancers, most of which (60%) were at an early stage of development [19]. The researchers pointed to the fact that most of the patients with idiopathic VTE and occult cancer was over the age of 70.

Rieu and collaborators [20] carried out a prospective analysis of 50 VTE patients, whose mean age was 80. Neoplasms were diagnosed in 4 VTE subjects (8%). Mortality over the 12-month follow-up period was 28%, and in 2 patients death was a direct consequence of the neoplastic disease. In their conclusions, the authors emphasised the lack of benefits stemming from an extensive oncological diagnostics in that group of patients. Medical interview, physical examination, routine lab tests, including blood count, transaminase activity, CRP, and creatinine, appeared to be sufficient. Determination of tumour markers was not recommended in that population, with the exception of PSA concentration in male subjects. Moreover, imaging examinations (abdominal ultrasound, chest X-ray, chest, abdominal cavity and pelvis CT) were not helpful in terms of detecting occult cancer at the time of VTE diagnosis.

In a yet another prospective randomized trial, involving a group of 201 idiopathic VTE patients, with no symptoms of neoplastic disease, Piccioli and collaborators [21] divided the study subjects into two subgroups. One of them underwent thorough testing for cancer, while the other one was only monitored in an outpatient setting. In the former subgroup cancer was detected in 13 patients at an early stage from the onset of a VTE episode, and in 1 patient during the following months of observation, whereas in the control group neoplastic disease was confirmed in 10 study subjects. During the 2-year follow-up period, 2 people from the extensively diagnosed group died of cancer, as compared with 4 persons from the control group. The researchers emphasised the significant role of chest, abdominal and pelvic CT in the diagnostics of occult cancer. Thanks to that imaging method alone 12 out of 14 neoplasms were detected, while with the use of tumour markers (CEA, CA125, α-FP, PSA) and an additional abdominal and pelvic ultrasound examination the result was 10 out of 14 cases. At the same time, the false positive results of tumour marker concentrations required further diagnostic tests in as many as 39 patients, which naturally increased the cost of the screening procedure. Implementation of an extensive oncological diagnostic algorithm resulted in the detection of the disease at a very early stage, and much better therapeutic options. Still, yet again a beneficial impact of such a management protocol on patient prognosis has not been proven. Therefore, the question of whether all idiopathic VTE patients should undergo a thorough oncological diagnostic process remains an unanswered one.

Within the space of many years, different oncological screening strategies have been elaborated for patients with idiopathic VTE. No universal management pattern has been agreed on, though. The cost of an extended diagnostic process may also give rise to controversy.

In one of their analyses, Di Nisio and collaboraters [22] conclude, making use of the SOMIT study data, that abdominal and pelvic CT (with or without mammography) together with sputum cytology is cost-effective and clinically viable in idiopathic VTE patients. At the same time, the authors emphasize lower usefulness of ultrasonography, fecal occult blood, and colonoscopy in detecting occult cancer. An interesting idea brought up by Di Nisio is the introduction of a term denoting the number of patients requiring extensive diagnostics in order to detect one neoplasm (***number needed to screen,*** NNTS). NNTS values have been calculated by means of dividing the number of all diagnosed patients by the number of patients with confirmed neoplastic disease. Such calculations have been carried out in all of the subgroups following differing diagnostic strategies (Table 1). The lowest value of NNTS involved the patients who were diagnosed in accordance with the following pattern: abdominal CT + mammography + sputum cytology + tumour markers. To each patient with confirmed cancer there were two in need of further oncological diag-

nostics. The problem appeared in all of the subgroups including tumour marker analysis in their diagnostic algorithm.

A relatively new imaging technique, i.e. whole-body positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) is a promising method for the identification of occult cancer in idiopathic VTE patients. FDG-PET combined with CT appears to be a more sensitive diagnostic method than each of the examinations alone [23–27]. In the first prospective cohort study, involving a group of 40 subjects, Matthew and collaborators made use of FDG-PET as a screening procedure for occult cancer in idiopathic VTE patients [28]. The study also involved a cost analysis, as based on FDG-PET, abnormalities (enlarged lymph nodes, non-specific nodules) were diagnosed in 62.5% of patients, requiring further verification by means of other techniques. CT prevailed amongst the additional examinations, as an adjunctive method, serving the purpose of final assessment of the suspicious lesions. None of the patients in whom neoplastic lesions had been excluded on the basis of FDG-PET/CT developed a proliferative disease within the two-year follow-up period. The researchers emphasised the safety of the performed procedures, and a diagnostic strategy comparable to others in terms of finances [22, 28, 29]. It is worth adding that further studies, involving a greater population of patients, and a longer follow-up period, are indispensable in order to evaluate the impact of FDG-PET screening on the reduction of mortality.

SUMMARY

There are no universal management patterns in terms of screening tests for occult cancer in idiopathic VTE patients. According to the clinical practice guidelines elaborated by the European Society for Medical Oncology (ESMO), it is recommended (recommendation II C) for the diagnostics of occult cancer in VTE patients to include the clinical interview and physical examination, chest X-ray, fecal occult blood, and urologic and gyna-

TABLE 1.

Diagnostic Model modified from Di Nisio and collaborators [22].

	Diagnostic strategy	NNTS	ND	NH
1.	abdominal/pelvic CT	9.9	10	1
2.	abdominal/pelvic CT + mammography	9.0	11	1
3.	abdominal/pelvic CT + sputum cytology	9.0	11	1
4.	abdominal/pelvic CT + tumour markers	9.0	10	26
5.	abdominal/pelvic CT + mammography + sputum cytology	8.3	12	1
6.	abdominal/pelvic CT + mammography + sputum cytology + tumour markers	7.6	13	26
7.	abdominal/pelvic CT + FOBT	9.0	11	15
8.	abdominal/pelvic CT + colonoscopy	9.0	11	4
9.	abdominal/pelvic US	19.8	5	1
10.	abdominal/pelvic US + mammography	16.5	6	1
11.	abdominal/pelvic US + sputum cytology	16.5	6	1
12.	abdominal/pelvic US + tumour markers	12.4	8	26
13.	abdominal/pelvic US + mammography + sputum cytology	14.1	7	1
14.	abdominal/pelvic US + mammography + sputum cytology + tumour markers	10	9	26
15.	abdominal/pelvic US + FOBT	16.5	6	15
16.	abdominal/pelvic US + colonoscopy	16.5	6	4
17.	CEA, CA-125, α-FP, PSA + FOBT	16.5	6	45
18.	CEA, CA-125, α -FP, PSA	16.5	6	29
19.	CEA, CA-125, α-FP	19.8	5	23

NNTS (number needed to screen) – number needed to screen to detect one patient with cancer; ND (number detected) – total number of cancer patients detected by extensive screening in the cohort; NH (number harmed) – total number of the patients evaluated further because of an eventually, benign condition in the cohort; CT – computed tomography, CA – cancer antigen; CEA – carcinoembryonic antigen; FOBT – fecal occult blood tests, α-FP – α-fetoprotein, PSA – prostate specific antigen; US – ultrasonography.
The data in table are based on the study cohort of 99 patients.

ecological consultation in male and female patients respectively [30]. Tumour markers, computed tomography, and endoscopic examinations should only be considered in carefully selected cases. Such an approach may seem controversial in the context of some of the published data (e.g. Di Nisio and collaborators [22]). So far, not a single clinical study with adequate methodology has been published, proving that the effort aimed at detecting occult cancer in VTE patients can improve overall prognosis, and survival in particular. The ESMO recommendations fail to take into account the criterion of a VTE idiopathic episode.

Due to the expected high negative predictive value, and ever greater availability of FDG-PET/CT, the examination is becoming more and more popular as part of the diagnostic process for occult cancer in idiopathic VTE patients. Combining different diagnostic procedures, involving CT, FDG-PET, MRI, and endoscopic tests, one can achieve very high sensitivity of occult cancer detection in idiopathic VTE patients. However, there have been no prospective studies on the matter to date.

In all of the studies, the need for further and longer (minimum 5 years) analysis of a large group of idiopathic VTE patients is emphasised, combined with a mortality reduction assessment (fundamental principle of screening tests). So far, cohort studies with 2-year follow-up period have been carried out. The cost incurred as a result of excessively extensive diagnostics may give rise to controversy.

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