Clin Appl Thrombosis/Hemostasis, 7(4):321–324, 2001

Original Report

Idiopathic Deep Vein Thrombosis and Subsequent Cancer: Suggestions for a Patient-Oriented and Practical Approach

Antonio Girolami, M.D.

University of Padua Medical School Department of Medical and Surgical Sciences, Second Chair of Medicine, Padua, Italy.

Summary: The relationship between an idiopathic deep vein thrombosis and a cancer is well established. It is not clear yet whether all patients with an idiopathic deep vein thrombosis should be thoroughly investigated for an occult cancer or only some. As a matter of fact, once a physician is faced with a patient who has an idiopathic deep vein thrombosis, three approaches are possible, mainly: 1) a wait and see approach; 2) a limited investigation; and 3) an extensive or invasive investigation. No sure criteria for the selection of the patients who should be extensively investigated are available. Suggestions have been made in this regard. Negative family or personal history for thrombosis, advanced age, deep vein thrombosis of upper limbs, existence of silent deep vein thrombosis in contralateral leg, tendency to relapse and/or to migrate, constitutional symptoms, or smoking may represent important clues that may justify an extensive study. This patient-oriented approach is mainly based on the experience of the caring physician.

The existence of a clear relation between deep vein thrombosis (DVT) and cancer is well established (1–9). Even the existence of a hypercoagulable state in patients with different forms of cancer has been widely accepted (10,11). Two large epidemiologic studies in Sweden and Denmark that were based on the National Registers of these two countries have given important support to the relation between DVT and a subsequent development of cancer (12,13).

Finally, a recent study has shown that patients with cancer who present with deep vein thrombosis have a poor prognosis (14). Because of the known value of early diagnosis for any cancer, it is important that the significance of this paraneoplastic syndrome is promptly recognized. A decision-analysis program based on mathematical methods has also been proposed to improve results (15), but does not seem to be practical.

Today, there are several opinions regarding the best approach to follow for the study of a patient with idiopathic DVT.

The patient is treated with unfractionated heparin (UH) or low-molecular-weight heparin for 6 to 10 days, and then is usually anticoagulated with Coumarin drugs for a 3- to 6-month period. However, the definition of "idiopathic" may be elusive because it depends on the exclusion of known risk factors, both congenital and acquired. This is of paramount importance because different results are obtained according to the extent this definition. Several conditions have to be excluded by careful history, physical examination, and laboratory tests (Table 1) before concluding that a thrombosis is idiopathic. Whereas clinical conditions as gathered from history or physical examination have remained practically unchanged throughout the years, unless a different awareness on the part the physician is present, congenital predisposition to thrombosis has changed considerably during the past few decades. Currently, it has become cumbersome and expensive to rule out all known coagulation prothrombotic defects. However, this evaluation has to be carried out lest a DVT be considered idiopathic. The significance of all these conditions varies; the antithrombin deficiency is the most serious, whereas the G to A 20210 prothrombin abnormality is most likely the least severe. At least antithrombin, protein C and protein S deficiencies, and factor V Leiden are usually excluded in all cases. Remaining conditions are often overlooked. The possibility that the mildest of these defects or other still unknown clotting defects may contribute to the occurrence of a DVT in a patient with an occult cancer has to be considered. In this case, the DVT could be considered as only partially idiopathic, but no study is available on the subject. Because it has been shown that cancers are more frequently diagnosed in the follow-up examination of all patients with DVT, regardless of the type,

Address correspondence and reprint requests to Prof. Antonio Girolami, Department of Medical and Surgical Sciences, Via Ospedale 105, 35100 Padova, Italy.

TABLE 1. *Conditions to be ruled out to define a DVT as idiopathic*

Congenital	Acquired
Antithrombin defects	Traumas
Protein C and protein S defects	Intravenous therapies
Factor V Leiden	Immobilization for any reason
Heart failure	Recent surgery
Fibrinolytic system defects	Fractures, casts, splints
Homocysteinemia	Pregnancy
20210 G to A prothrombin abnormality	OCT
	APA syndrome
	Hyperviscosity syndrome

DVT, deep vein thrombosis; OCT, oral contraceptive therapy; APA, antiphospholipid antibodies.

one could speculate that all patients should be extensively investigated and followed up. Needless to say, this type of examination is not feasible. Unfortunately, often no investigation is carried out and the patient is only controlled to measure the level of anticoagulation.

It has been shown that in the follow-up of these patients, the diagnosis of cancer is not uncommon. Often the diagnosis is made when metastases are already present.

Therefore, the problem entails the need either for a limited search or for an extensive or invasive approach.

The matter has not been solved because several strategies have been proposed (16,17). A "wait-and-see" approach is not advisable. A limited investigation is often followed, but several neoplasias may be missed that could have been diagnosed at an early stage. Extensive investigation has often to be ruled out for several reasons, namely 1) poor patient compliance; 2) high cost; and 3) risk associated with invasive procedures.

In recent years, we have been following up several patients with idiopathic DVT by means of a patient-tailored approach. This approach is based on the following facts and observations:

1. Realization that an extensive and aggressive approach cannot be applied to every patient for reasons of cost, availability of tests, and patient compliance.
2. The observation that the most frequent cancers found after an idiopathic DVT are those of the colon, prostate, pancreas, lung, breast, and ovary.

TABLE 2. *Coagulation-related factors that may justify an extensive investigation*

Resistance to anticoagulant therapy
Tendency to relapse
Tendency to migrate
Coexistence of DVT together with superficial venous thrombosis
Presence of upper limb thrombosis
Increased platelet number
Existence of silent DVT in contralateral limb

DVT, deep vein thrombosis.

TABLE 3. *Main non–coagulation-related factors indicating or justifying the need for an extensive or invasive diagnostic approach*

Smoking
Negative family history for thrombosis
Negative personal history for thrombosis
Positive neoplastic markers (e.g., TPA, CEA, PSA)
↑ ESR, ↑ LDH, ↑ alkaline phosphatase
Anemia
Constitutional symptoms (e.g., weight loss, sweating, fever)
Advanced age

TPA, tissue plasminogen activator; CEA, carcinoembryonic antigen; PSA, prostate-specific antigen; ESR, erythrocyte sedimentation rate; LDH, lactic dehydrogenase.

3. Careful evaluation of some signs, symptoms, and routine laboratory tests.
4. Frequent association of idiopathic upper limb thrombosis with cancer (18).
5. Frequent presence of silent controlateral DVT in patients with cancer and DVT of one leg (19).
6. Awareness that life expectancy in the case of colon, lung, breast, and ovarian cancers is mainly influenced by early detection.

Such a limited, patient-oriented approach could be the best approach, but guidelines are not yet fully established (16,17).

The main conditions in which our opinion could warrant extensive studies in a given patient are listed in Tables 2 and 3. These conditions are either coagulation related or noncoagulation related, and could be considered as potential cofactors that could enhance the probability of an association with an idiopathic thrombosis.

A careful search for these conditions has to be carried out in every patient. The most important of these events are resistance to anticoagulant therapy, tendency to relapse, or recurrence. Presence of silent DVT in contra-

TABLE 4. *Limited versus extensive (invasive) approach for the search of an occult cancer in a patients with idiopathic DVT*

Limited	Extensive (invasive)
Medical history	Same as limited approach plus
Physical examination	Serial evaluation of all neoplastic markers
Routine laboratory tests (ESR)	Total body CAT
Peripheral blood cells, nonspecific markers (e.g., alkaline phosphatase, LDH)	Colonoscopy
	Broncoscopy
Main neoplastic markers (CEA, TPA, Ca 19-9)	Gastroscopy
	Gastrointestinal series
Chest radiograph	Prostate sonography and biopsy
Abdominal sonography	Bone marrow
	Mammography
	Laparoscopy
	Mediastinoscopy

DVT, deep vein thrombosis; ESR, erythrocyte sedimentation rate; CAT, computed axial tomography; LDH, lactic dehydrogenase; CEA, carcinoembryonic antigen; TPA, tissue plasminogen activator.

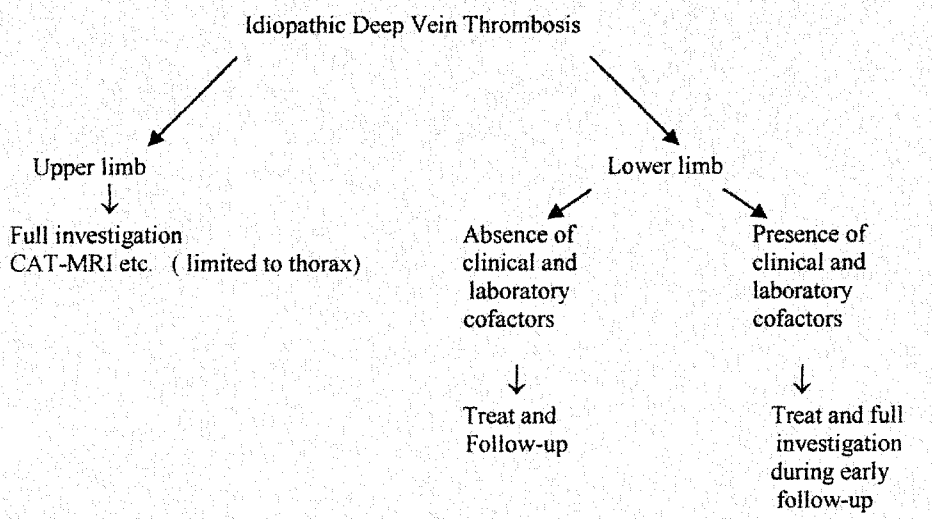

FIG. 1. Simplified flow chart for the treatment of idiopathic deep vein thrombosis. CAT, computed axial tomographic scan; MRI, magnetic resonance imaging.

lateral leg and DVT of the upper limb are also conditions suggesting an occult cancer (18,19).

Among the non–coagulation-related conditions, smoking and advanced age seem to be of great importance.

Whenever more than one of these conditions is present, an extensive investigation may be justified.

The main procedures needed compared with what is indicated for a limited approach are summarized in Table 4. These procedures could be carried out even on an outpatient basis and during the anticoagulation period, if attention is given to the potential danger of bleeding complications. Colonoscopy, broncoscopy, and esophagogastroduodenoscopy with possible need for biopsies should be carried out after discontinuation or during an interruption of anticoagulant therapy. It is interesting to note that in both retrospective and prospective studies, the critical period for the appearance of a cancer is 6 to 12 months after the idiopathic DVT (9,12,13). Such a relatively short period seems to indicate that the cancer was really an occult cancer—namely, a cancer that could not be detected but was already present. This clearly indicates that the idiopathic DVT but could really be considered as a paraneoplastic syndrome.

The results of recent studies seem to favor an extensive approach (20). However, we think that a reasoned patient-tailored approach may yield similar results. This can also be briefly illustrated in Figure 1, which emphasizes the different significance of upper limb thrombosis and lower limb thrombosis. It has been demonstrated that DVT of upper limbs is frequently associated with tumors of the lung or mediastinum (19). In this case, an extensive work-up is always indicated (e.g., computed axial tomography, magnetic resonance imaging, mediastinoscopy).

In conclusion, the decision to follow a limited or an extensive approach is based on both objective criteria and the experience of the caring physician, whose expertise in vascular diseases and oncology and diagnostic ability play an important role in the final decision (21,22).

REFERENCES

1. Aderka D, Brown A, Zelikovski A, et al. Idiopathic deep vein thrombosis in an apparently healthy patient as a premonitory sign of occult cancer. *Cancer* 1986;57:1847.
2. Ahmed Z, Mohyuddin Z. Deep vein thrombosis as a predictor of cancer. *Angiology* 1996;47:261.
3. Bastounis EA, Karayiannakis AJ, Makri GG, et al. The incidence of occult cancer in patients with deep venous thrombosis: a prospective study. *J Intern Med* 1996;239:153.
4. Cornuz J, Pearson SD, Creager MA, et al. Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep venous thrombosis. *Ann Intern Med* 1996 15;125:785.
5. Monreal M, Fernandez-Llamazares J, Perandreu J, et al. Occult cancer in patients with venous thromboembolism: which patients, which cancers. *Thromb Haemost* 1997;78:1316.
6. Monreal M, Lafoz E, Casals A, et al. Occult cancer in patients with deep venous thrombosis: a systemic approach. *Cancer* 1991;67: 541.
7. Monreal M, Salvador R, Soriano V, et al. Cancer and deep vein thrombosis. *Arch Intern Med* 1998;148:485.
8. Nordstrom M, Lindblad B, Anderson H, et al. Deep venous thrombosis and occult malignancy: an epidemiological study. *BMJ* 1994; 308:891.
9. Prandoni P, Lensing AW, Buller HR, et al. Deep-vein thrombosis and the incidence of subsequent symptomatic cancer. *N Engl J Med* 1992;327:1128.
10. Luzzatto G, Shafer A. The prothrombotic state in cancer *Semin Oncol* 1990;17:147.
11. Girolami A, Mootse G, Cliffton EE. Blood plasminogen (profibrinolisyn) levels in patients with leukemia and lymphoma *Am J Med Sci* 1967;254:334.
12. Baron JA, Gridley G, Weiderpass E, et al. Venous thromboembolism and cancer. *Lancet* 1998;351:1077.
13. Sorensen HT, Mellemkjaer L, Steffensen H, et al. The risk of a diagnosis of cancer after primary deep venous thrombosis or pulmonary embolism. *N Engl J Med* 1998;338:1169.
14. Sorensen HT, Mellemkjaer L, Olsen JH, et al. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000 21;343:1846.
15. Barosi G, Marchetti M, Dazzi L, et al. Testing for occult cancer in patients with idiopathic deep vein thrombosis: a decision analysis. *Thromb Haemost* 1977;78:1319.

16. Prandoni P, Piccioli A, Girolami A. Cancer and venous thromboembolism: an overview. *Hematologica* 1999;84:437.
17. Prandoni P. Antithrombotic strategies in patients with cancer. *Thromb Haemost* 1997;78:141.
18. Girolami A, Prandoni P, Zanon E, et al. Venous thromboses of upper limbs are more frequently associated with occult cancer as compared with those of lower limbs. *Blood Coagul Fibrinolysis* 1999;10:455.
19. Prandoni P, Lensing AW, Piccioli A, et al. Ultrasonography of contralateral veins in patients with unilateral deep-vein thrombosis. *Lancet* 1998;352:786.
20. Piccioli A, Lensing AWA, Prandoni P. Screening for occult malignancy in patients with idiopathic venous thromboembolism (SOMIT). Study design. *Thromb Haemost* 1997;(Suppl):PS489.
21. Rajan R, Levine M, Gent M, et al. The occurrence of subsequent malignancy in patients presenting with deep vein thrombosis: results from a historical cohort study. *Thromb Haemost* 1998;79:19.
22. Girolami A. Idiopathic versus secondary thrombosis as a predictive marker of occult malignancy. *Thromb Haemost* 1998;80:206.