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A SELF-TEST ON A CLINICAL CASE

A 43-year-old woman with chest pressure

A 43-year-old woman presents to the emergency department with substernal chest pressure of moderate intensity that started approximately 6 hours ago. The pressure radiates to both arms and is accompanied by nausea. She says she has had no emesis, diaphoresis, fevers, chills, shortness of breath, abdominal pain, melena, dysuria, weight loss, headaches, change in vision, seizures, joint pain, or skin rashes. She also says she has had no prior similar episodes and has no history of myocardial infarction (MI) or stroke.

The patient has a history of gastroesophageal reflux disease and uterine fibroids. She has had three pregnancies, one ending in spontaneous abortion at 12 weeks and two ending with healthy children delivered by cesarean section. She does not take any daily medications. She has smoked one pack per day over the last 25 years. She denies using alcohol or illicit drugs.

The patient's mother had idiopathic deep vein thrombosis (DVT) at age 46, her father had an MI at age 65, and her sister had an MI at age 43.

On examination, she is in mild distress but is alert and oriented. Her temperature is 99.0°F (37.2°C), blood pressure 98/66 mm Hg, heart rate 65 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 99% on room air. Her body mass index is 19.5 (normal range 18.5–24.9). Her skin appears normal. Her head and neck show no obvious abnormalities, lymphadenopathy, thyromegaly, or bruits. Her heart, lungs, and abdomen are normal, as are her strength, sensation, reflexes, and gait.

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Laboratory values at the time of admission:

- White blood cell count 12.58 × 10^9/L (reference range 4.0–11.0)
- Hemoglobin 15.4 g/dL (12.0–16.0)
- Platelet count 122 × 10^9/L (150–400)
- International normalized ratio (INR) 1.1 (0.9–1.1)
- Activated partial thromboplastin time 29.1 seconds (24.6–34).

A heart attack, and then a stroke

An initial electrocardiogram shows normal sinus rhythm, left anterior hemiblock, and nonspecific T-wave abnormalities. Cardiac enzymes are measured at intervals: her troponin T level is less than 0.01 ng/mL at the time of admission but rises to 0.75 ng/mL 3 hours later (normal range 0.0–0.1 ng/mL). Similarly, her creatine kinase-MB level is 3.3 ng/mL at admission but rises to 71.9 ng/mL 3 hours later (normal range 0.0–8.0 ng/mL).

She has acute chest discomfort, a 25-pack-year smoking history, and a family history of MI and DVT

The patient is diagnosed with non-ST-elevation MI. An intravenous heparin drip is started, and she is sent for urgent cardiac catheterization, which shows a total occlusion in a lateral obtuse marginal branch of the left circumflex artery due to a thrombus in the vessel. Otherwise, her coronary arteries are angiographically free of disease. The heparin drip is continued, and treatment is started with abciximab (ReoPro) and tissue plasminogen activator (Alteplase). She is sent to the cardiac intensive care unit for recovery, where she is placed on continuous cardiac monitoring, with no evidence of arrhythmia.

One day later, the left side of her face is drooping, her left arm is weak, and her speech is slurred. Magnetic resonance imaging of

TABLE 1

Risk factors for arterial occlusion

Thrombosis
Aneurysm thrombus
Atherosclerosis
Entrapment syndrome
Hypercoagulable state
Low-flow state
Vascular grafts

Embolism
Arterial source
- Atherosclerotic plaque
- Aneurysm

Cardiac source
- Atrial fibrillation
- Atrial myxoma
- Endocarditis
- Myocardial infarction
- Paradoxical embolism
- Prosthetic valve
- Valvular disease

Trauma
Blunt
Iatrogenic
Penetrating

After discharge, she has three new DVTs, despite therapeutic INRs

the brain shows an acute ischemic infarct in the right temporoparietal area and multiple areas of subacute to chronic ischemia. Magnetic resonance angiography of the brain indicates patent vessels. Both transthoracic and transesophageal echocardiography are performed and indicate normal left ventricular size, ejection fraction of 55%, valves without thrombus or vegetations, aorta with mild atheroma, and no patent foramen ovale by Doppler flow or agitated saline contrast study. Carotid artery Doppler ultrasonography shows 40% to 59% stenosis bilaterally.

ARTERIAL THROMBOSIS

1 Which of the following is a risk factor for arterial thrombosis?

- ☐ Atherosclerosis
- ☐ Protein C deficiency
- ☐ Use of oral contraceptive pills
- ☐ The factor V Leiden mutation

Protein C deficiency, the use of oral contraceptives, and the factor V Leiden mutation are typically associated with venous thrombosis[1]; they have been documented as a cause of arterial thrombosis only in some case reports. In contrast, atherosclerosis is a well-established risk factor for arterial thrombosis.

Arterial occlusion can be due to thrombosis, embolism, or trauma

The causes of arterial occlusion can be categorized as thrombotic, embolic, or traumatic (TABLE 1).

Atherosclerosis is a risk factor for thrombosis and can be a source of emboli. Atherosclerotic plaque rupture may release inflammatory mediators, which also predispose to thrombosis.[2] This patient's coronary arteries are essentially free of atherosclerotic disease per angiography. However, studies of intravascular ultrasonography have shown that coronary angiography may not detect all atherosclerotic plaques, as angiography can show only the lumen of the artery and not the plaque itself.[3] For that reason, atherosclerosis has not been ruled out completely, and further workup is needed to evaluate other possible causes of her thrombotic events.

Embolism is the most likely cause of her stroke, however. Cases of arterial embolism can be classified on the basis of the origin of the thrombus, ie, the heart, an artery, or the venous system via a patent foramen ovale (paradoxical embolism). This patient's echocardiogram reveals mild aortic atheroma, which can be a source of emboli, especially soon after intervention.

Case continues: Acute and recurrent DVT

While recovering from her MI and stroke, the patient develops edema and pain in both legs. Doppler ultrasonography is performed, which reveals acute DVT in the right gastrocnemius and posterior tibial veins and left soleal vein, despite her continued heparin therapy.

Her platelet count is 189×10^9/L, so heparin-induced thrombocytopenia is not suspected; the new DVT is thought to be due to her hospitalization. Several days later, oral warfarin (Coumadin) is started and titrated to an INR of 2.0 to 3.0, the heparin is phased out, and the patient is sent home.

In the first few months after discharge, the patient presents to the emergency department

three times with severe leg pain, and each time she is found to have extensive DVT in various leg veins even though she is complying with her warfarin therapy. At each visit, her INR is in the range of 2.5 to 3.1.

Comment. Her recurrent DVT warrants further evaluation for risk factors for venous thrombosis, which can be divided into hereditary and acquired factors.

Hereditary risk factors include the factor V Leiden mutation, the prothrombin gene mutation, hyperhomocysteinemia, dysfibrinogenemia, and deficiencies of protein C, protein S, and antithrombin.

Acquired risk factors include the antiphospholipid antibody syndrome, cancer, immobilization, surgery, congestive heart failure, pregnancy, use of hormonal contraceptives, hormone replacement therapy, nephrotic syndrome, trauma, and infection.[1,4]

TESTING FOR HYPERCOAGULABLE STATES

2 In view of our patient's recurrent thrombotic episodes, should she be tested for hypercoagulable states?

- ☐ Yes
- ☐ No

Testing for hypercoagulable conditions is warranted if it will affect the patient's management or outcome. Some authorities recommend testing patients who are clinically characterized as "strongly" thrombophilic,[5] ie, those who present with DVT and are younger than age 50, have recurrent thrombotic episodes, have a first-degree relative with documented thromboembolism before age 50, or have thrombotic episodes despite warfarin therapy.

This patient should be tested for hypercoagulable conditions because her initial DVT occurred before age 50 (at age 43), she has had recurrent, apparently idiopathic thrombotic episodes, she has a family history of thromboembolism, and she had clots while on therapeutic warfarin therapy, all of which suggest a hypercoagulable state. Furthermore, the confirmation of her diagnosis may affect her medical management, as it may determine if further testing and therapies are needed.

Case continues: Tests are negative

Laboratory tests for hypercoagulable conditions are performed and are negative for the factor V Leiden mutation, the prothrombin gene mutation, antithrombin deficiency, and protein C and S deficiencies. A screen for antiphospholipid antibodies is indeterminate.

TREATMENT AFFECTS TEST RESULTS

3 If a patient is on warfarin therapy, which test results may be affected?

- ☐ Antithrombin levels
- ☐ Protein C and S levels
- ☐ Factor V Leiden mutation

Warfarin decreases the levels of proteins C and S; therefore, the levels of these substances cannot be accurately interpreted in a patient taking warfarin.

All anticoagulants prolong the clotting time and may affect the results of assays based on the clotting time, such as the prothrombin time, the partial thromboplastin time, the dilute Russell's viper venom time (DRVVT), the hexagonal phase phospholipid neutralization assay, the thrombin time, and clottable protein C and protein S. Heparin reduces the level of antithrombin; however, laboratories now have heparin-binding agents that reduce the effect of heparin in clotting studies.

Testing is warranted if it will affect the patient's management or outcome

Acute thrombotic states lower the levels of antithrombin and proteins C and S.

Assays not based on the clotting time (immunogenic or genetic tests such as those for anticardiolipin antibodies and the factor V Leiden and prothrombin gene mutations) are not affected by anticoagulant use.[5]

However, the presence or absence of a hypercoagulable state should not affect the treatment of acute DVT, and a full 6- to 12-month course of anticoagulation should be completed.[6,7] If possible, lupus anticoagulant testing should be repeated 2 weeks after anticoagulation is stopped.[8]

This patient needs lifelong anticoagulation because of her repeated thrombotic episodes. Stopping the medication for 2 weeks for testing would increase the risk of rethrombosis in this patient, and most experts would not advise it.

TABLE 2

Results of our patient's tests for antiphospholipid antibodies

TEST*	PATIENT'S VALUE	NORMAL REFERENCE
Beta-2 glycoprotein I IgG	< 9 SGU	< 20 SGU
Beta-2 glycoprotein I IgM	< 9 SMU	< 20 SMU
Cardiolipin IgG	< 9 GPL	0–40 GPL
Cardiolipin IgM	< 9 MPL	0–40 MPL
Cardiolipin IgA	< 9 APL	0–40 APL

*Antibodies against beta-2 glycoprotein I and cardiolipin can be detected and measured in sera using the enzyme-linked immunosorbent assay (ELISA) and are the most commonly tested antibodies. Immunoglobulin G (IgG) or IgM antibodies against beta-2 glycoprotein I are considered significant at levels > 20. IgG, IgM, or IgA anticardiolipin antibodies are considered significant when > 40. Beta-2 glycoprotein I IgG and IgM and cardiolipin IgG antibodies are the most specific for thrombosis; cardiolipin IgM antibodies are often seen in other inflammatory or infectious processes. SGU = standard IgG units, SMU = standard IgM units, GPL = IgG antiphospholipid units, MPL = IgM antiphospholipid units, APL = antiphospholipid units.

In summary, testing for hypercoagulable conditions is not recommended during an acute thrombotic episode and is preferably performed while the patient is not on anticoagulation therapy. If the patient is already on anticoagulation, the results of tests for hypercoagulable conditions should be interpreted with caution.

Our patient lost 10 lb in 4 months, smokes, and has had several DVTs, so testing for cancer is appropriate

Case continues: Another stroke

During the subsequent year, the patient's primary care physician monitors her warfarin use and sends her for age-appropriate cancer screening, including a breast examination, Papanicolaou smear, and mammography. Also, given her history of smoking, a chest radiograph is ordered. All of these studies are normal. In addition, evaluations for hematologic disorders such as myelodysplastic syndrome, polycythemia vera, and Waldenström macroglobulinema reveal normal complete blood counts and normal results on serum and urine protein electrophoresis.

Later that year, she returns to the emergency department with complete aphasia and total right-sided paralysis. Magnetic resonance imaging shows an acute infarct in the left frontal operculum, a subacute infarct in the right cerebellum, and multiple chronic cortical and subcortical infarcts throughout the brain. Ultrasonography shows an extensive new DVT in her right leg. Her INR at this time is 3.1.

WHAT CONDITIONS CAUSE BOTH ARTERIAL AND VENOUS THROMBOSIS?

4 Given that the patient has evidence of both recurrent arterial and venous thromboses, which of the following conditions is likely?

- ☐ Antiphospholipid antibody syndrome
- ☐ Heparin-induced thrombocytopenia
- ☐ Malignancy
- ☐ All of the above

Conditions associated with both arterial and venous thrombosis include antiphospholipid antibody syndrome, heparin-induced thrombocytopenia, malignancy, paradoxical embolism, hyperhomocysteinemia, myeloproliferative disorders, myelodysplastic disorder, paraproteinemia, vasculitis, and paroxysmal nocturnal hemoglobinuria.[1,4]

The hypercoagulability associated with malignancy is also known as Trousseau syndrome. This term was originally used to describe migratory thrombophlebitis as a forewarning for occult visceral malignancy, and has grown over the years to describe malignancy-induced hypercoagulability.[9]

At present, the exact mechanism that causes Trousseau syndrome is unknown. Some hypotheses implicate mucin (produced by the cancer),[10] tissue factor,[11] tumor-associated cysteine proteinase,[12] tumor hypoxia,[13] and oncogene activation as plausible triggers for this syndrome.

TABLE 3

Results of our patient's lupus anticoagulant panel

TEST*	PATIENT'S VALUE	NORMAL REFERENCE
Activated partial thromboplastin time	59.3 sec	24.6–32.8 sec
International normalized ratio	3.2	0.8–1.2
Circulating anticoagulant (immediate inhibitor)	Positive	Negative
Platelet neutralization	Positive	Negative
DRVVT screen	57.8 sec	24.9–39.7 sec
DRVVT confirm ratio	1.19 sec	0.99–1.2 sec
DRVVT 1:1 mix	36.5 sec	24.9–39.7 sec
Hexagonal phase screen	78.0 sec	38.5–66.5 sec
Hexagonal phase confirm	64.1 sec	45.7–63.8 sec
Hexagonal phase delta	13.9 Δ sec	< 6.7 Δ sec
Factor VIII level	82%	49–134%

*The subcommittee on Lupus Anticoagulants and Anti-Phospholipid Antibodies of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) established the criteria for the diagnosis of lupus anticoagulant in 1995. The criteria include the following:
1) A prolonged phospholipid-dependent clotting test (screening test);
2) Evidence of an inhibitor (1:1 mix of patient:normal plasma);
3) Evidence that the inhibitor is phospholipid-dependent; and
4) Exclusion of specific inhibitors (Brandt et al[14]).
Ideally, testing should be avoided during acute phase and, if possible, should be done with the patient off of anticoagulants. If the patient is tested while on heparin, laboratories now have heparin-binding agents that reduce the effect of heparin in the sample. Thrombin time can be used to detect the effect of direct thrombin inhibitors. Warfarin also may affect the results of clotting-time-based assays. The panel includes:
a) Three screening assays: if these tests are positive, it could be due to either clotting factor deficiency or an inhibitor. Activated partial thromboplastin time, DRVVT screen, and hexagonal phase screens are clotting-time-based assays that can be prolonged in antiphospholipid antibody syndrome. The DRVVT and hexagonal phase screens are more specific for antiphospholipid antibodies than the standard activated partial thromboplastin time.
b) Two mixing studies: both the circulating anticoagulant and the DRVVT 1:1 mix can confirm the presence of an inhibitor, if the prolonged screening clotting time does not correct.
c) Three assays to confirm phospholipid dependence, meaning that the inhibitor is specifically an antiphospholipid antibody: the DRVVT confirm ratio, hexagonal phase confirm, and hexagonal phase delta. These tests involve repeating the clotting time assays using phospholipid-rich reagents. If antiphospholipid antibodies are present, they will be partially neutralized, and the clotting time should normalize or shorten.
The DRVVT confirm ratio is the ratio of the screening DRVVT to the DRVVT confirm clotting time. The hexagonal phase delta is the change in the clotting times between the hexagonal phase screen and the hexagonal phase confirm test.
d) The presence of other inhibitors can be ruled out by testing the factor VIII level (if normal or elevated, it indicates no factor VIII inhibitor) and thrombin time to rule out the presence of prothrombin inhibitor, direct thrombin inhibitors (bivalirudin or argatroban), or indirect thrombin inhibitor (heparin).

Trousseau syndrome: hypercoagulability due to cancer

As stated above, the patient has a normal platelet count and negative results on cancer screening tests. Tests for antiphospholipid antibodies and lupus anticoagulant are repeated. Tests for the specific antiphospholipid antibodies against beta-2 glycoprotein I and cardiolipin are negative (TABLE 2). However, the test for lupus anticoagulant is positive by the criteria of the International Society on Thrombosis and Haemostasis: the patient has a prolonged clotting time screening test (hexagonal phase screen, DRVVT screen), positive mixing study (DRVVT 1:1 mix and circulating anticoagulant), positive phospholipid dependence (hexagonal phase screen, confirm, and delta; DRVVT confirm ratio; and platelet neutralization procedure), and no evidence of other factor-specific inhibitors (TABLE 3).[14]

DOES SHE HAVE ANTIPHOSPHOLIPID ANTIBODY SYNDROME?

5 The patient is positive for lupus anticoagulant. Does she have antiphospholipid antibody syndrome?

- ☐ Yes
- ☐ No
- ☐ Repeat testing is needed to meet the diagnostic criteria

The Sapporo criteria[15] indicate that antiphospholipid antibody syndrome is present if at least one clinical criterion and one laboratory criterion are met. The clinical criteria are one or more episodes of arterial or venous thrombosis or pregnancy-related morbidity, ie:

- Unexplained intrauterine fetal death at 10 weeks gestation or later with no apparent fetal abnormality
- Premature births of a morphologically normal fetus at less than 34 weeks of gestation due to preeclampsia, eclampsia, or placental insufficiency
- Three or more spontaneous abortions at 10 weeks of gestation or earlier, with no known paternal chromosomal abnormalities or maternal hormonal abnormalities and normal maternal anatomy.

The laboratory criteria are:

- Lupus anticoagulant present
- Anticardiolipin antibody (IgG or IgM) titer greater than 40 IgG antiphospholipid units (GPL) or IgM antiphospholipid units (MPL) or higher than the 99th percentile of the testing laboratory normal reference range
- Anti-beta-2 glycoprotein-I antibody (IgG or IgM) titer greater than 20 GPL or MPL or higher than the 99th percentile of the testing laboratory normal reference range.

The patient likely has antiphospholipid antibody syndrome because her lupus anticoagulant screen is positive and she meets the clinical criteria of thrombosis, and she should continue to be treated accordingly. However, to officially meet the revised Sapporo criteria, she would need to have laboratory tests that are positive on two or more occasions at least 12 weeks apart.

To date, no evidence supports extensive cancer screening after idiopathic thrombosis

Case continues: Lung cancer is found

The patient reports that she has lost 10 pounds in 4 months. Since age-appropriate cancer testing was previously performed, a more extensive evaluation for weight loss is undertaken, with computed tomography of the chest, abdomen, and pelvis. These tests reveal a nodule in the right upper lobe of the lung, scarring in the right middle and left lower lung lobes, and hilar lymphadenopathy. Bronchoscopy with transbronchial biopsy confirms that she has adenocarcinoma of the lung.

6 What is suggested as a sufficient workup for malignancy in patients with idiopathic venous thromboembolism?

- ☐ Computed tomography of the chest, abdomen, and pelvis for every patient with idiopathic venous thromboembolism
- ☐ Positron emission tomography and tumor marker levels
- ☐ A comprehensive history and physical examination, routine laboratory tests, chest radiography, age- and sex-specific cancer screening, and patient-specific testing as indicated clinically

To date, there is no evidence to support a cancer evaluation beyond a comprehensive medical history and physical examination, routine laboratory testing, chest radiography, and age- and sex-specific cancer screening unless it is dictated by the patient's clinical presentation. A study by Cornuz et al[16] suggested that this approach is appropriate for detecting cancer in patients with idiopathic venous thromboembolism.

A 2004 study[17] attempted to answer the question of what to do about patients who have idiopathic venous thromboembolism but no other signs or symptoms that raise any clinical suspicion of cancer. This study randomized patients with idiopathic venous thromboembolism to undergo either routine medical management or an extensive malignancy evaluation. The evaluation included ultrasonography of the abdomen and pelvis, computed tomography of the abdomen and pelvis, gastroscopy or a double-contrast barium swallow study, colonoscopy or sigmoidoscopy followed by a barium enema, stool occult blood testing, and sputum cytology. Women were also tested for the tumor markers carcinoembryonic antigen, alpha-fetoprotein,

and CA-125, and they underwent mammography and Papanicolaou testing; men were tested for prostate-specific antigen and underwent ultrasonography of the prostate. The results of the study did not reveal a statistically significant survival benefit in the group that underwent extensive cancer evaluation.

These studies indicate that the decision to test for cancer should be guided by clinical suspicion. Our patient lost 10 pounds in 4 months, smokes, and has had recurrent venous thromboembolism, so testing was appropriate.

After her diagnosis with adenocarcinoma of the lung, the patient has yet another DVT despite an INR of 3.1 and treatment with warfarin and aspirin.

LOW-MOLECULAR-WEIGHT HEPARIN FOR PATIENTS WITH CANCER?

7 True or false? Low-molecular-weight heparin is more effective than warfarin in preventing DVT in cancer patients without increasing the bleeding risk.

☐ True
☐ False

This statement is true. The American College of Chest Physicians (ACCP) recommends immediate treatment of DVT with low-molecular-weight heparin for 6 to 12 months after a thrombotic event in a patient with malignancy.[6,18]

Two major studies provide evidence for these recommendations: the Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer (CLOT)[19] and the Trial of the Effect of Low-Molecular-Weight Heparin Versus Warfarin on Mortality in the Long-Term Treatment of Proximal Deep Vein Thrombosis (LITE)[20] studies.

The CLOT[19] study showed that dalteparin (Fragmin) 200 IU/kg subcutaneously once daily for 1 month and then 150 IU/kg once daily was more effective than oral warfarin titrated to an INR of 2.5 and did not increase the risk of bleeding.

The LITE trial[20] showed the efficacy of tinzaparin (Innohep) 175 IU/kg subcutaneously daily, which can be used as an alternative.

Enoxaparin sodium (Lovenox) 1.5 mg/kg once daily has also been used. However, if low-molecular-weight heparin is not available, warfarin titrated to an INR of 2 to 3 is also acceptable.[18]

The ACCP consensus panel recommends giving anticoagulation for an initial 6 to 12 months and continuing it as long as there is evidence of active malignancy.[6] The American Society for Clinical Oncology also recommends placement of an inferior vena cava filter for patients who have contraindications to anticoagulation or for whom low-molecular-weight heparin fails.[18]

Case continues: Summing up

In conclusion, our patient had an underlying malignancy, causing Trousseau syndrome. Before her cancer was diagnosed, she also had test results that suggested antiphospholipid antibody syndrome. Both of these conditions likely contributed to her hypercoagulable state, increasing her propensity for clotting and causing her recurrent thrombosis. The patient is currently on low-molecular-weight heparin and is undergoing palliative chemotherapy for metastatic adenocarcinoma of the lung. To this date, she has not had any new thrombotic events.

The ACCP recommends treatment for 6 to 12 months initially, then for as long as the patient has cancer

TAKE-HOME POINTS

- Risk factors for arterial occlusion can be divided into thrombotic, embolic, and traumatic categories.
- Risk factors for venous thrombosis can be divided into hereditary and acquired categories.
- Evaluation for hypercoagulable conditions is recommended if it will affect patient management or outcome. Patients to be considered for testing include those with idiopathic DVT and who are under age 50, those with a history of recurrent thrombosis, and those with a first-degree relative with documented venous thromboembolism before age 50.
- Evaluation for hypercoagulable conditions should ideally be performed either before starting anticoagulation therapy or 2 weeks after completing it.

- Potential causes of both arterial and venous thrombosis include antiphospholipid antibody syndrome, cancer, hyperhomocysteinemia, heparin-induced thrombocytopenia, paradoxical emboli, myeloproliferative disorders, myelodysplastic syndrome, paraproteinemia, vasculitis, and paroxysmal nocturnal hemoglobinuria.
- Current evidence does not support an extensive cancer evaluation in patients with idiopathic venous thromboembolism, unless dictated by the patient's clinical condition.
- In patients with venous thromboembolism and active malignancy, anticoagulation is recommended for at least 6 to 12 months and as long as there is evidence of active malignancy. ■

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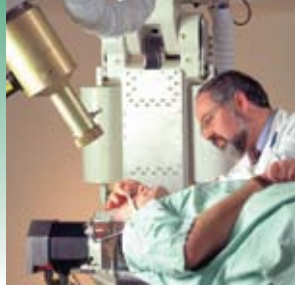

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