We prospectively studied 78 consecutive patients with acute pulmonary embolism (PE) to determine the most appropriate workup study for searching for hidden cancer. After a careful physical examination, the following tests were performed: erythrocyte sedimentation rate (ESR), complete blood cell counts, biochemistry, carcinoembryonic antigen levels, chest radiograph, upper gastrointestinal endoscopy, and abdominal ultrasound. If a malignant lesion was suspected, further appropriate tests were performed. After hospital discharge, periodic follow-up was performed on all patients in our outpatient clinic. A malignant lesion was detected in 9 of 78 patients: in 7 of them, cancer was diagnosed during the hospital admission because of acute PE. All but one of these 7 patients were asymptomatic, except for PE symptoms. In three of them some abnormalities on physical examination led to the diagnosis of cancer; in the remaining three patients the diagnosis was suspected from abnormal results of blood tests. Cancer was detected several months after hospital discharge in two additional patients: an esophageal cancer was diagnosed 5 months later in one of the 23 patients who refused endoscopy; and a colonic carcinoma was detected 21 months after hospital discharge in a patient in whom colonoscopy was not performed at the time of hospital admission. When considered overall, cancer was more commonly found in patients with “idiopathic” PE as compared with patients with known risk factors for PE development (6 of 21 patients vs 3 of 51 patients; p<0.05). On the other hand, one patient died because of massive recurrent PE after a biopsy sample was obtained because of a prostatic node. Gross hematuria had developed shortly after biopsy, and any attempt to increase heparin doses was followed by recurrent hematuria. According to our experience, any decision about procedures that potentially involve bleeding should be carefully individualized in patients with acute PE.

(Ches 1993; 103:516-19)

Venous thromboembolism (VTE) has been associated with virtually all cancers, especially with gastrointestinal, urogenital, and lung neoplasms. Although usually developing in advanced stages of the disease, not infrequently VTE (both pulmonary embolism [PE] and deep venous thrombosis [DVT]) may appear before the cancer has become symptomatic and may lead to an earlier diagnosis of cancer. In the last decade, increasing attention has been focused on this relationship, and several reports have confirmed a strong association between VTE and subsequent cancer.

The relationship between DVT in the lower extremities and hidden cancer has been clearly demonstrated. Several prospective studies have been performed, and patients without any known risk factors for thrombosis have been identified as being at an increased risk of occult cancer. Otherwise, there are only a few studies in which patients with PE were investigated for cancer; probably because the number of patients with PE is quite a bit lower than the figure for DVT. However, since both DVT and PE may be considered different manifestations of the same disease (VTE), it would not be surprising that the same underlying conditions could be present in patients with either PE or DVT.

We recently reported our experience with an intensive workup study searching for hidden cancer in a consecutive series of patients with DVT. A malignant neoplasm was detected during hospital admission in 12 of 113 DVT patients. Cancer was more commonly found in patients with idiopathic DVT, and some cases of cancer were at a very early stage. Malignancy would not have been recognized in some patients if such a workup study had not been performed. Simultaneously, the same workup study was applied to a series of patients with PE. Since in our previous study the cancer in some patients was only detected several months after hospital discharge, we did not conclude the present study until the last patient came to our outpatient clinic 1 year after discharge.

Methods

Patients

From June 1987 to June 1991, 100 consecutive patients were diagnosed as having PE in our hospital. Of these patients, 22 had evidence of previous cancer and were then excluded from the present investigation. There were 34 male and 44 female subjects,
aged 30 to 89 years (mean, 67 years). Fifty-one of these 78 patients (65 percent) had one or more of the following known risk factors for thromboembolism: recent surgery, bed rest, leg varicosities, or a history of VTE. For the remaining 27 patients, no predisposing factors were found, and they were considered to have “idiopathic” PE.

Methods

All patients had objective tests to confirm the diagnosis: PE was considered in patients with clinical symptoms, high-probability defects on ventilation-perfusion lung scan (according to the criteria of Biello et al.), and venographic documentation of venous thrombosis in the lower extremities. Thus, patients with high-probability lung scans but normal venograms were not included in the study. After PE diagnosis was confirmed, and heparin therapy was started at conventional doses, special care was paid to any symptoms suggestive of malignancy, and a thorough physical examination was performed.

The screening laboratory tests included erythrocyte sedimentation rate (ESR), complete blood cell counts, peripheral blood smear examination, liver function tests, serum protein electrophoresis, lactate dehydrogenase (LDH), and carcinoembryonic antigen (CEA). Additionally, a chest radiograph, abdominal ultrasonography, and upper gastrointestinal endoscopy were routinely proposed during hospital admission on all patients. After hospital discharge, one or more of the above tests led us to suspect cancer, as shown in Table 1. The tumor was detected at a very early stage (less than 5 cm, no nodes involved) in three patients: patients 1, 5, and 6. In two patients (patients 3 and 7), the tumor was easily resected, but had some nodes involved. In the remaining two patients, the malignancy was considered to be inoperable.

On the other hand, a prostatic node was detected on physical examination in a 79-year-old man in whom embolism developed shortly after an acute ischemic stroke. Results of all laboratory tests were normal, except for prostatic acid phosphatase levels, which were slightly increased (2.0 fold the upper normal levels). After discontinuation of heparin therapy, a needle biopsy was performed 18 days after PE. One day later, gross hematuria developed, and heparin was administered but at lower doses than required. Any attempt to increase heparin doses was followed by recurrent hematuria. The patient died suddenly 8 days after biopsy, and necropsy demonstrated that the cause of death was a large, massive PE. Pathologic studies of the prostatic node discovered a benign hyperplastic adenoma.

Additional Findings

Three patients were found to have adenomatous polyps (considered by most authors as a colorectal cancer precursor) by colonoscopy. Two large, benign tumors (ovarian cystadenoma, one; fibroma of the ovary, one) located in the pelvis were detected by ultrasonography in two women. The diagnosis was suspected in both cases on physical examination, and venography showed signs of extrinsic compression on

<p>| Table 1 — Clinical Characteristics of the Nine Patients With PE in Whom a Malignancy Was Found |
|-----------------------------------------------|--------|-------------------------------------------------|-----------------|--------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Patient No./Sex/Age, yr</th>
<th>Risk Factor</th>
<th>Symptoms of Cancer</th>
<th>Time of Diagnosis</th>
<th>Abnormal Findings*</th>
<th>Site of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/81</td>
<td>Idiopathic</td>
<td>No</td>
<td>1 wk</td>
<td>Anemia</td>
<td>Colon</td>
</tr>
<tr>
<td>2/F/68</td>
<td>Idiopathic</td>
<td>No</td>
<td>1 wk</td>
<td>ALT, AST</td>
<td>Liver</td>
</tr>
<tr>
<td>3/F/49</td>
<td>Idiopathic</td>
<td>No</td>
<td>1 wk</td>
<td>Pelvic mass</td>
<td>Ovary</td>
</tr>
<tr>
<td>4/M/82</td>
<td>Idiopathic</td>
<td>No</td>
<td>1 wk</td>
<td>Rectal examination</td>
<td>Prostate</td>
</tr>
<tr>
<td>5/M/70</td>
<td>Leg varicosities</td>
<td>Yes</td>
<td>2 wk</td>
<td>Lumbar pain</td>
<td>Prostate</td>
</tr>
<tr>
<td>6/F/85</td>
<td>Postoperative</td>
<td>No</td>
<td>2 wk</td>
<td>Breast node</td>
<td>Breast</td>
</tr>
<tr>
<td>7/M/44</td>
<td>Idiopathic</td>
<td>No</td>
<td>4 wk</td>
<td>CEA</td>
<td>Colon</td>
</tr>
<tr>
<td>8/F/59</td>
<td>Idiopathic</td>
<td>No</td>
<td>5 mo</td>
<td>Dysphagia</td>
<td>Esophagus</td>
</tr>
<tr>
<td>9/M/60</td>
<td>Postoperative</td>
<td>No</td>
<td>21 mo</td>
<td>Bleeding</td>
<td>Colon</td>
</tr>
</tbody>
</table>

*ALT = alanine aminotransferase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen.
the venous system. Furthermore, abnormally increased antiphospholipid antibodies were found in two additional patients. Finally, a monoclonal gammopathy was found in three patients, but both bone marrow biopsy specimen and bone scan failed to evidence myeloma.

**Follow-up**

All patients have been followed up in our outpatient clinic. One of them, a 59-year-old man with "idiopathic" PE, complained about rapidly progressing dysphagia and anorexia 5 months after hospital discharge. He was one of the 23 of 78 patients who had refused endoscopy at the time of hospital admission. On readmission, the test was performed, and an esophageal carcinoma with severe narrowing of the lumen was found. He died a few days after surgery. Another patient, a 60-year-old man, complained about rectal bleeding 21 months after hospital discharge. Colonoscopy was then performed and a well-differentiated, ulcerating adenocarcinoma was found 20 cm from the anus. Both patients were asymptomatic for cancer at the time of hospital admission; results of physical examination and routine blood tests were normal, as well as abdominal sonography and CT scan. Colonoscopy was not performed in the latter patient because of normal CEA levels and because he did not complain about any change in bowel habits. Since it is likely that cancer was present at the time of PE, the patient diagnosed as having colon cancer at 21 months was included in the "occult cancer" group.

For the remaining patients, no evidence of malignancy was found during follow-up. Herein the three patients with "benign gammopathy" are included.

**Validity of the Workup Study**

Both an accurate physical examination and routine blood tests proved to be useful in detecting abnormalities that ultimately led to the diagnosis of a malignant lesion. Recognition of a pelvic mass on palpation of the abdomen (one patient), a prostatic node on rectal examination (two patients), or a breast node (one patient) were important clues to achieve a final diagnosis of cancer in some patients. Mild abnormalities in results of liver function tests, a microcytic anemia, and a mild increase in CEA levels led to pursuing malignancy in three additional patients (Table 1).

On the other hand, cancer was not recognized in two patients, and the diagnosis was then delayed until symptoms appeared. Gastroedoduodenoscopy was not performed in the patient with esophageal carcinoma as he refused to undergo endoscopy. Colonoscopy was not performed in the patient with a colonic carcinoma because he did not complain of any symptoms and because of normal CEA levels.

Cancer was significantly more common in patients with idiopathic PE: 6 of 27 patients (22 percent) as compared with 3 of 51 patients with secondary PE (6 percent; \( p = 0.04 \), Fisher's Exact Test). Not only was cancer more common in patients with "idiopathic" PE, but also an underlying lesion (cancer or benign tumors, or the antiphospholipid syndrome) was again significantly more common in such patients (10 of 27 patients [37 percent] with "idiopathic" PE vs 6 of 51 patients [12 percent]; \( p < 0.01 \)), as shown in Table 2. Otherwise, no differences were found in terms of sex, age, ESR, LDH, or hemoglobin levels.

**DISCUSSION**

Seventy-two patients surviving acute, massive PE were retrospectively studied by Hall et al.\cite{12} in 1977. When reviewed 1 to 9 years later, there were 12 deaths, and the causes of death were malignant diseases in six patients. Of these six patients dying 3 months to 7 years later, three were not known to have malignant disease when they presented with massive embolism. Since then, several retrospective studies on patients with PE have been published,\cite{11,12,13} and a significantly higher frequency of subsequent cancer has been demonstrated in PE patients as compared to those considered for PE, but in whom such a diagnosis was ruled out. Thus, our aim was not to confirm these data, but to assess if there is a subgroup of PE patients at a higher risk of having occult cancer and to determine the most appropriate workup study.

We recently reported our experience with an intensive workup study for searching for occult cancer in patients with DVT in the lower extremities.\cite{6} We concluded that blood cell counts, LDH, chest radiographs, and abdominal ultrasonography (or CT

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients, No.</th>
<th>Cancer</th>
<th>Others*</th>
<th>Mean, mo</th>
<th>&gt;12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Bed rest</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Previous DVT/PE</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Leg varicosities</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>27</td>
<td>6</td>
<td>4</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>

*Adenomatous polyps in colon, three patients; benign pelvic tumors, two patients; anticardiolipin antibodies, two patients.

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**Table 2—Results of Prospective Study in Patients With PE, According to the Risk Factors for Thromboembolism**

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scan) should be routinely performed during hospital admission, particularly in those patients with idiopathic PE. Now, the usefulness of such an approach has also been studied in a series of patients with PE. Cancer has been found in a similar percentage of patients (9 of 78 patients, 11.5 percent). However, several aspects merit comment.

First, it seems clear that patients without any known risk factors for PE should be thoroughly investigated, not only for cancer, but also for a number of benign, premalignant, or other diseases, such as the primary antiphospholipid syndrome. As for the diagnosis of cancer, a careful physical examination searching for a pelvic mass seems to be mandatory. At variance with our previous study in DVT patients, LDH levels were not useful in PE patients; this was probably due to normal levels often being high in such patients. By contrast, because of the high incidence of colon carcinoma (as well as adenomatous polyps) in our series, CEA levels should be routinely determined, even when normal levels are not adequate to exclude cancer. Should all patients with idiopathic PE be examined by endoscopy? We do not have an answer to this question. However, in the literature, these neoplasms are not infrequently found. Ironically, Armad Trousseau (the first author to report the association between VTE and hidden cancer) died of gastric cancer that presented as a case of idiopathic thrombosis.13

Furthermore, another question arises from the case of the patient with a prostatic node in whom discontinuation of heparin therapy resulted in massive recurrence of PE and death. How aggressive should an investigation for cancer be in this kind of patient? Should any aggressive procedure be delayed for some time, until anticoagulant therapy may be discontinued? Certainly, patients with acute PE are at an increased risk of recurrences,14,16 and discontinuation of heparin therapy would clearly increase the probability of such recurrences. Again, an unfortunate case has enabled us to draw some conclusions. According to our experience, any decision about procedures that potentially involve bleeding should be carefully individualized in patients with acute PE.

In summary, we found cancer to be present in 9 of 78 patients with acute PE. Eight of these nine patients were asymptomatic, with the exception of PE symptoms: physical examination led to the diagnosis of cancer in three patients, microcytic anemia and high CEA levels led to the suspicion of colon cancer in one, isolated abnormal CEA levels were evident in 1, and abdominal ultrasonography showed one case of hepatocarcinoma. However, cancer was misleading in two otherwise healthy PE patients because gastrointestinal endoscopy was not performed (one case) or because colonoscopy did not seem to be indicated (one patient).

As in our previous study in DVT patients, both malignant and benign tumors were more commonly found when no identifiable predisposing conditions for thrombosis were present (idiopathic PE). However, there is an important aspect at variance with our previous study: since PE patients are more prone to recurrences after discontinuation of heparin therapy, some aggressive procedures could be contraindicated.

Given the cost and logistics of performing all these tests, this approach requires closer scrutiny of the cost/benefit implications in a larger group of patients. In any case, since hidden cancer appears to be more common in patients with idiopathic PE (one out of four or five patients), we suggest that only these patients should be thoroughly investigated.

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