Cardiac Metastases in Lung Cancer*

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Cardiac metastases from bronchogenic carcinoma are not commonly diagnosed prior to death. This study isolates factors associated with the development of cardiac involvement. Four hundred eighteen consecutive patients with lung cancer who had autopsies were studied. Twenty-five percent of these patients had cardiac involvement. Factors associated with cardiac metastases were (1) histologic cell type of the tumor, (2) aggressive therapy, (3) extent of disease, and (4) tumor differentiation. The presence of cardiac metastases was not related to the length of survival. Clinical signs of cardiac involvement included an enlarging heart on the chest x-ray film, development of congestive heart failure, or electrocardiographic changes. Suspicion of cardiac metastases in high-risk individuals, prompt diagnostic evaluation, and rapid institution of therapy may improve the outlook for many patients, since reaccumulation of fluid was generally slow.

Lung cancer will account for approximately 80,000 deaths in the United States in 1976. Important strides have been made to improve the quality of life and extend survival in patients with this disease, however, in spite of sophisticated diagnostic techniques, unrecognized cardiac metastases are still a significant cause of morbidity and mortality in these patients. This study attempts to isolate factors associated with the development of cardiac metastases so that earlier diagnoses may be anticipated and appropriate regimens of treatment planned.

MATERIALS AND METHODS

Four hundred eighteen patients with lung cancer who had autopsies at the Veterans Administration Hospital, Washington, DC, over a ten-year period were studied. Of these patients, 114 had been treated on protocol studies of the NCI-VA Medical Oncology Section from December 1969 to July 1973. The treatments consisted of aggressive polychemotherapy, primarily using cyclophosphamide, mechloretamine (nitrogen mustard), methotrexate, and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), with or without radiotherapy. The remaining 304 patients received some form of supportive therapy or radiotherapy. Less than 1 percent received a curative or palliative surgical procedure.

Protocols of autopsies and slides were reviewed for all patients. Slides were stained with hematoxylin-eosin. Mucicarmine stained slides were available in a number of cases. Pertinent gross and microscopic data concerning cardiac involvement were recorded in each case.

All patients from protocol studies were evaluated prior to the onset of therapy as to whether they had regional or extensive disease. Regional disease is tumor confined to one hemithorax with or without involvement of the ipsilateral mediastinal and supraclavicular lymph nodes. Extensive disease is tumor that has spread to the contralateral lung or to distant extrathoracic sites. These designations were confirmed or changed at autopsy.

Length of survival was calculated from the day of diagnosis to the day of death.

Thirty-eight patients from protocol studies had evidence of cardiac metastases at autopsy. The clinical records of 32 of these patients were available for review. Six clinical records could not be located. An additional 66 patients not on protocol had cardiac metastases at autopsy.

Lung tumors were classified according to the WP-L Lung Cancer Classification. Epidermoid carcinomas show evidence of formation of epithelial pearls, individual cell keratinization, formation of intercellular bridges, nesting, and stratification. Tumors showing only stratification are excluded from this group. A distinction is made between well and poorly differentiated tumors, depending on the abundance or sparsity of diagnostic markers. Small cell carcinomas include both small, round lymphocyte-type cells with naked nuclei and indistinct nucleoli, as well as the somewhat larger, more spindled, fusiform or polygonal types of cells which on occasion attempt tubular or rosette formations. Adenocarcinomas form acinar or glandular patterns, with or without papillary structures, regardless of the bronchopulmonary source of the tumor. Tumors elaborating mucin but showing no attempt at gland formation are excluded from this category. Large cell anaplastic carcinomas include all tumors which show no evidence of differentiation and include those tumors which stratify and produce mucin. A number of tumors of all types had prominent formation of giant cells. These tumors were evaluated separately.

RESULTS

Pathology

The gross and microscopic characteristics of the 38 protocol patients with cardiac metastases are summarized in the following paragraphs.

Eight (21 percent) of 38 patients with epidermoid carcinoma had metastases (Table 1). Two of
the eight had limited disease. Four had moderately to well differentiated tumors, and four had poorly differentiated tumors with prominent anaplastic components. The pericardium was grossly involved in six of the eight cases, presenting as a thick fibrotic adhesive pericarditis or as nodular metastases. The myocardium was involved in six cases. Small nodular masses were identified grossly in five. In one case, there was massive replacement of 70 to 80 percent of the myocardium by tumor. Two of the cases with both pericardial and myocardial involvement had a significant accumulation of pericardial fluid (100 ml and 250 ml).

Six (24 percent) of 25 patients with small cell carcinoma had cardiac involvement. All six had extensive disease. The pericardium was involved in all cases. The gross pathologic findings varied from an adhesive pericarditis to a frankly nodular infiltrate measuring up to 2 cm in diameter. The myocardium was involved grossly in two cases. In one case the heart muscle was massively replaced by tumor. Pericardial effusion (200 ml and 500 ml) occurred in two cases. In both cases the pericardium and myocardium were grossly invaded by tumor. Fourteen (41 percent) of 34 patients with adenocarcinoma had cardiac metastases. Only one of these patients had limited disease. Six had poorly differentiated or anaplastic tumor components. The pericardium was involved in all but one case. In six cases the pericardium was converted into a thick pannus measuring up to 2 cm in width, admixed with fibrous or gelatinous material. In three cases, only microscopic tumor was identified. The myocardium was involved grossly in four cases and microscopically in three additional cases. A tumor thrombus was adherent to the left ventricle in one case. Only one case with pericardial involvement had a significant bloody effusion (100 ml) at the time of autopsy.

Ten (59 percent) of 17 patients with large cell carcinoma had cardiac involvement. All patients had extensive disease. Eight of the ten had pericardial disease identified grossly as fibrous or fibrous pericarditis, with occasional small identifiable nodules. Seven of the ten had myocardial nodules measuring from 3 to 5 mm or had microscopic evidence of lymphatic invasion. Two of the ten had emboli adherent to the endocardium in the right and left sides of the heart. Only one patient with pericardial metastases had a significant accumulation of fluid (300 ml).

Overall, 104 (25 percent) of the entire 418 patients with lung cancer who were studied had cardiac metastases at autopsy. Of this total group, 91 patients had pericardial metastases, and 47 had myocardial metastases.

Clinical Findings

The diagnosis of cardiac involvement was not suspected before death in 27 of the 32 patients for whom complete clinical records were available (records for six patients had been lost). In five of the 32 patients the diagnosis was suspected because of development of symptoms of acute congestive failure or because of sudden enlargement of the cardiac shadow on the chest x-ray film. Pericardial taps yielded positive cytologic findings in two of the five patients, which caused the diagnosis to be made. Both patients were treated with repeated pericardial taps and radiotherapy and improved sufficiently to be discharged from the hospital. In neither of these patients did pericardial symptoms recur. The diagnosis was suspected, but not made, in three patients.

Of the 27 patients in whom the diagnosis was not suspected, eight had clinical signs or symptoms which retrospectively were suggestive of cardiac metastases (seven with acute congestive failure and one with paradoxical pulse). Eleven of the 27 patients had nonspecific electrocardiographic findings of sinus tachycardia or changes in the ST-T wave. One patient had cardiomegaly on chest x-ray examination. Six of the 27 patients had no ECG within one month of death. Only one of the 27 patients with cardiac metastases had no clinical signs or symptoms and had normal findings on ECG and chest x-ray film.

Of the 11 patients with nonspecific electrocardiographic findings, the numbers of patients with each finding were as follows: sinus tachycardia, ten patients; ST-T changes, one patient; low voltage, three patients; left axis deviation, two patients; left bundle branch block, two patients; right bundle-branch block, two patients; atrial fibrillation, two patients; myocardial infarction as the terminal event, two patients; premature atrial contractions, one patient; premature ventricular contractions, one patient; atrial flutter, one patient; short P-R interval, one patient; and normal ECG, one patient.

The median survival of patients with and without cardiac metastases was determined by histologic cell type. No differences in survival were found.
Thus, increased survival did not appear as a predisposing cause of cardiac disease in this population.

Clinically, there appear to be differences in the frequency of cardiac involvement by histologic cell type (Table 1). The incidence of pericardial and myocardial involvement in patients with large cell carcinoma is greater than for those with either epidermoid ($P < 0.01$) or small cell carcinoma ($P < 0.025$). The difference in incidence between large cell carcinoma and adenocarcinoma is not statistically significant. The difference in incidence between patients with adenocarcinoma, compared with epidermoid or small cell carcinoma, is not statistically significant, but comparing adenocarcinoma to pooled data for epidermoid and small cell carcinoma approaches significance ($P = 0.08$).

Comparing the incidence of cardiac metastases among patients in the protocol studies vs patients not on protocol, an increased incidence for protocol patients with adenocarcinoma and large cell carcinoma was statistically significant ($P = 0.05$ and $P = 0.02$, respectively). Furthermore, when one looks at the incidence of cardiac metastases for protocol patients with limited vs extensive disease (Table 2), there is an increased incidence among patients with extensive disease.

Tumor differentiation was also examined, as shown in the following tabulation giving numbers of patients (numbers within parentheses are percentages):

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Limited</th>
<th>Extensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermoid carcinoma</td>
<td>4/32 (13)</td>
<td>6/20 (30)</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>4/6 (67)</td>
<td>0/25 (4)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>8/24 (33)</td>
<td>6/10 (60)</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>3/6 (50)</td>
<td>0/17 (6)</td>
</tr>
</tbody>
</table>

Cardiac metastases occur more often with poorly differentiated tumors than with moderately differentiated tumors. An overall $\chi^2$ test comparing poorly vs moderately differentiated tumors adjusted for cell type gave a value of $P = 0.002$. The highest frequency of cardiac metastases occurred in patients with large cell anaplastic carcinoma, with or without giant cells.

Patients who had a combination of factors were at the highest risk; for example, among the patients who had large cell anaplastic carcinoma containing giant cells and who had extensive disease and received aggressive protocol treatments, the incidence of cardiac metastases was 64 percent (7/11).

In cases where cardiac metastases occurred, the pericardium was more frequently involved than the myocardium (Table 3). Interestingly, there was more myocardial involvement in patients who received aggressive protocol therapy than in those who did not. This was true for epidermoid carcinoma, adenocarcinoma, and large cell carcinoma, although not for small cell carcinoma.

The use of radiation therapy to the chest and mediastinum was equal in protocol and nonprotocol patients with cardiac metastases. Fourteen (37 percent) of 38 protocol patients with cardiac metastases received radiation therapy in doses greater than 4,000 rads as part of their primary therapy, as did 28 (42 percent) of 68 nonprotocol patients.

**Discussion**

Metastatic tumors to the heart are 20 to 40 times more common than primary tumors. The tumors most commonly metastatic to the heart are melanoma (44 percent), leukemia (44 percent), breast cancer (33 percent), lung cancer (31 percent), and lymphoma (24 percent). The overall rate of 25 percent in this study is consistent with other autopsy series indicating an incidence of 15 to 35 percent for cardiac metastases in patients with lung cancer. Previous authors have found only minor differences in the incidence of cardiac metastases by

| Table 2—Limited vs Extensive Disease in All Protocol Patients* |
|-----------------|-----------------|-----------------|
| Cancer          | Limited         | Extensive       |
| Epidermoid carcinoma | 2/18 (11)     | 6/20 (30)       |
| Small cell carcinoma | 0               | 6/25 (24)       |
| Adenocarcinoma     | 1/6 (17)        | 13/28 (46)      |
| Large cell carcinoma | 0               | 10/17 (59)      |

*Table values are numbers of patients; numbers within parentheses are percentages.

| Table 3—Metastases to Pericardium vs Myocardium* |
|----------|-----------------|-----------------|
| Tumor Type | Pericardium | Myocardium |
| Epidermoid | 6/8 (75) | 6/8 (75) |
| Small cell | 6/6 (100) | 2/6 (33) |
| Protocol   | 13/14 (93) | 12/14 (86) |
| Adenocarcinoma | 13/14 (93) | 7/14 (50) |
| Nonprotocol | 16/16 (100) | 5/16 (31) |
| Large cell anaplastic | 8/10 (80) | 7/10 (70) |
| Protocol   | 11/16 (69) | 3/16 (19) |

*Table values are numbers of patients; numbers within parentheses are percentages.
cell type; however, none has separated as a distinct cell type the large cell anaplastic carcinomas, which appear to have a predilection for cardiac involvement in the face of aggressive therapy.

Cardiac metastases were more common in patients with extensive disease. This is not surprising, since by definition, patients with extensive disease are more likely to have multiple metastatic foci in intrathoracic or extrathoracic sites.

The higher incidence of cardiac metastases among patients with poor tumor differentiation is more impressive than what Senoo\(^8\) reported. This is not unexpected, since such tumors tend also to metastasize widely and, by extrapolation, would produce more cardiac involvement.

Our experience that pericardial involvement is more common than myocardial involvement is similar to that of other investigators;\(^7\),\(^8\),\(^12\) however, patients who received aggressive protocol treatment had more myocardial involvement than those not on protocol. This suggests that aggressive therapy may alter the metastatic potential of the tumors, possibly by an immunosuppressive effect. Why small cell carcinomas do not respond in this fashion is unclear, although it may relate to the greater sensitivity of small cell carcinoma to chemotherapy.

Our ability to make an antemortem diagnosis in only two (5 percent) of 38 patients with cardiac metastases is consistent with the historical difficulty in making this antemortem diagnosis. Studies by Dimmette\(^14\) and by Harrer and Lewis\(^15\) reported antemortem diagnosis in only 4 percent of a large group of patients who had cardiac metastases at autopsy (21/500 and 7/147, respectively). Even in our five patients with clinical pericardial effusion, the histologic diagnosis of cardiac metastases could be made only in two (40 percent). This was similar to the experience of Cohen et al\(^16\) with nine patients who had signs of cardiac compression, with the diagnosis confirmed in only three (33 percent).

The pericardial effusion associated with tumor is of a variable nature. Scott and Garvin\(^10\) reported five simple effusions, seven bloody effusions, three purulent effusions, and 11 serofibrinous effusions in 26 malignant pericardial effusions. Cohen et al\(^16\) reported seven clear effusions, four bloody effusions, and three serosanguinous effusions in 14 similar effusions.

In the majority of our patients (27/32), cardiac metastases were not even suspected; however, there were a substantial number of patients (8/27) with either increasing congestive heart failure or paradoxical pulse. In these patients, diagnosis could and should have been entertained, particularly if high-risk factors were considered.

Cardiac metastases may be the ultimate pathogenesis for demise, primarily because of the potential of inducing uncontrollable congestive heart failure or transient lethal abnormalities in conduction. Studies by Kline\(^11\) and by Harrer and Lewis\(^15\) have reported uncontrollable congestive heart failure as the cause of death in up to 33 percent of patients with metastatic tumor to the heart. Scott and Garvin\(^16\) reported several patients with arrhythmias, most of whom had involvement of the atria. A substantial number of our patients with whom there were no other clinical findings had nonspecific electrocardiographic abnormalities.

Alteration of cardiac oxygen supply and oxygen consumption, causing myocardial infarction, is another possible mechanism of death. Two of our 38 patients with cardiac metastases died of myocardial infarction, which is almost identical to the experience of Malaret and Aliaga,\(^17\) in which two of 38 patients with cardiac metastases from all tumor types had myocardial infarction as the cause of death. A rare cause of myocardial infarction is direct invasion of a coronary artery by the tumor. There is one report of such a case by Franciosa and Lawrison,\(^18\) which occurred in a patient with poorly differentiated squamous cell carcinoma of the lung. Alternatively though, Kline\(^11\) reported that seven of 20 patients with cardiac metastases had chest pain and dyspnea suggestive of myocardial infarction, but none had myocardial infarction at autopsy.

It thus appears that cardiac metastases represent an important source of morbidity and mortality in patients with lung cancer. Suspicion of this complication and prompt vigorous attempts at diagnosis are necessary. Treatment consists of pericardiocentesis to relieve symptoms and signs of impending cardiac tamponade, followed by radiation therapy or chemotherapy, depending on the sensitivity of the tumor. Both of our patients with diagnosed pericardial metastases were successfully treated to the extent that they were able to leave the hospital, and they had no further cardiac symptoms for the remainder of their clinical course.

References
5 Frichard RW: Tumors of the heart: Review of the subject and report of 150 cases. Arch Pathol 51:98-128, 1951
6 Bisel HF, Wroblewski F, LaDue JS: Incidence and clinical manifestations of cardiac metastases. JAMA 153:712-715, 1953
10 Scott RW, Garvin CF: Tumors of the heart and pericardium. Am Heart J 17:431-436, 1939
15 Harrer WY, Lewis PL: Metastatic tumors involving the heart and pericardium. Pa Med 74:57-60, 1971

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