Pathology and survival in operable cases of giant-cell carcinoma of the lung

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SYNOPSIS Giant-cell carcinoma of the lung is usually rapidly fatal and nearly all of the published cases have been described on the basis of postmortem findings. The surgical specimens from three resected giant-cell carcinomas are described and the subsequent courses of the patients are summarized. A further nine surgically treated cases have been found in the literature. Giant-cell carcinoma of the lung is thought to be an anaplastic variant of adenocarcinoma and its aggressive behaviour is a reflection of its degree of anaplasia. Despite the aggressive behaviour of this type of cancer, patients may survive for many years if the tumour is resected.

Giant-cell carcinoma of the lung is generally considered to be a particularly lethal form of cancer. The first detailed account of this type of tumour is that of Nash and Stout (1958) and the literature now includes over a 100 cases. However, Hadley and Bullock (1953) appear to be the first authors to use the term 'giant cell' carcinoma; they reviewed a series of 84 carcinomas of the lung and classified six of them as spindle- and giant-cell tumours.

Many authors have emphasized the shortness of the interval which separated the onset of symptoms and the patient's death and the only long-term survivor to be found in the literature is a patient described by Kern, Jones, and Chapman (1968). This patient's primary tumour was resected and he was still alive eight years after the operation; this is unusual, for there are few accounts of the behaviour of this type of tumour in surgically treated patients. In nearly all of the published cases of giant-cell carcinoma the tumour has been inoperable and the diagnosis has usually been made only after a necropsy. This paper describes the pathological features of three of these tumours as found in surgical specimens and the fate of the patients after operation. Although this series is small, it does provide some information about the pathology and behaviour of giant-cell carcinoma of the lung at a stage when the tumour is still operable.

CASE REPORTS

CASE 1 The patient was a man of 28 who complained of intermittent pain in the chest and had had occasional haemoptyses over a period of six months. He smoked between 20 and 40 cigarettes a day. He had been investigated at another hospital for tuberculosis and had been referred to the University of Chicago Hospitals for further investigation. His Mantoux reaction was persistently negative and his chest radiograph revealed a large opacity in the left upper lung field. No malignant cells were found in the sputum. At a diagnostic thoracotomy performed by Dr P. V. Moulder a portion of the mass was submitted for frozen section which was interpreted as an anaplastic carcinoma. The left upper lobe and part of the left lower lobe were resected. The patient made a satisfactory recovery and was given a postoperative course of radiotherapy. He died at home six-and-a-half months after the operation and one year after the appearance of his initial symptoms. Death was attributed to carcinoma of the lung, but no necropsy was performed.

Pathology The anterior part of the apex of the upper lobe was replaced by a spherical tumour 6 cm in diameter. The tumour appeared to be well encapsulated and was divided into lobules by fibrous septa; there were areas of haemorrhage and necrosis.

Histologically, the tumour consisted of large oval and polygonal cells which, in the areas away from the fibrous septa, were supported by a very scanty inter-vening stroma. Many large multinucleated giant cells were present and some of these contained phagocytosed cellular remnants (Figs. 1 and 2). A few of the mononucleated tumour cells contained PAS-positive droplets, but they did not stain with Southgate's mucicarmine. No large strap-shaped cells were present and cross striations were not found. The fibrous capsule was dense and in places it was being infiltrated by the tumour (Fig. 3). The tumour appeared to have been removed completely and no metastases were found in the lymph nodes.

CASE 2. The patient was a man of 71 years who was...
FIG. 1. Part of the tumour from case 1. There is little stroma between the tumour cells. Some of the cells are large and multinucleated. One cell contains the phagocytosed remnants of another cell. Haematoxylin and eosin x 480.

FIG. 2. Two of the tumour giant cells in a smear made from the cut surface of the tumour from case 1. The cells have many large nuclei with prominent nucleoli. Haematoxylin and eosin x 480.

FIG. 3. Part of the fibrous capsule of the tumour in case 1. At this point the appearance of encapsulation is due to thickening of the pleura. The tumour is invading the fibrous tissue and the surrounding fat. Haematoxylin and eosin x 30.
described as being a heavy cigarette smoker for over 40 years. He first presented in May 1966 complaining of a cough with haemoptysis for six months. The chest radiograph revealed a mass in the hilar region of the right lung and occlusion of the right pulmonary artery was shown by cardiac catheterization. The sputum contained abundant highly atypical cells which were regarded as being consistent with the presence of a malignant tumour. A thoracotomy was performed by Dr W. E. Adams who found the tumour in the right lower lobe which was then resected. Posteriorly the tumour involved the pleura which was adherent to the chest wall; there was no evidence of secondary deposits in the lymph nodes. His postoperative recovery was marked by an episode of bleeding from a duodenal ulcer; this required several blood transfusions. In December 1966 he was readmitted for the investigation of jaundice accompanied by pale stools; this appeared to be due to a viral hepatitis. The chest radiographs at this time showed an enlarging mass in the left lung which was thought to be a secondary deposit.

He made a satisfactory recovery from hepatitis but in March 1967, he became ill again. At this time, he had signs of cerebral irritation and it was thought that he possibly had cerebral metastases. He died suddenly in another hospital in July 1967, 13½ months after the thoracotomy and 19 months after the beginning of the illness. No necropsy was performed.

Pathology The specimen consisted of the right lower lobe with some separately submitted mediastinal lymph nodes. A tumour $3 \times 3 \times 3$ cm was present in the superior segment and extended into the superior segmental bronchus. The tumour was grey but had mottled areas of haemorrhage. The tumour was 3 cm from the cut end of the bronchus but it extended laterally to the pleural surface.

Histologically, the tumour consisted of two types of tissue. Much of the tumour had the typical appearance...
of a giant-cell carcinoma. In these areas the cells were large and polygonal with faintly eosinophilic foamy cytoplasm; there was little stroma in these parts of the tumour. The nuclei were large, vesicular, and contained very prominent nucleoli. Multinucleated cells were abundant in these areas (Fig. 4).

The other histological pattern was one of large cells with clear cytoplasm but with nuclei similar to those described above (Fig. 5). In these areas fewer multinucleated cells were present. The clear cells did not stain with Southgate's mucicarmine but some cells contained small PAS-positive granules. No metastases were found in the lymph nodes.

CASE 3. This patient was a man of 67 who was referred to the University of Chicago Hospitals for radiotherapy in March 1968. At the age of 56, in 1957, a right upper lobectomy had been performed at Ravenswood Hospital. He was known to be a cigarette smoker but no more details of this stage of the history are available. (I am grateful to Dr Harry Hetz for the use of the histological material from this case and for supplying a description of the tumour which was removed in 1957.)

Pathology The resected lobe contained a grey tumour $9 \times 7.5$ cm which was invading the lumen of the right upper lobe bronchus. The pleura was not involved, but the tumour extended to the resected margin of the bronchus.

The tumour was made up of sheets of large anaplastic cells with little fibrous stroma. The nuclei were large and contorted and there was a diffuse sprinkling of binucleated and trinucleated cells. Focally there were collections of very large and very bizarre cells with eosinophilic cytoplasm and evidence of phagocytosis (Fig. 6). Some cells had PAS-positive droplets in their cytoplasm and very occasionally there were mucicarmine-positive droplets. There was no evidence of either squamous or glandular differentiation anywhere in the tumour. In places the tumour was infiltrated by lymphocytes. No metastases were found in the hilar lymph nodes but the bronchopulmonary nodes were involved by direct extension.
Subsequent course The patient remained well for 11 years until, one month before his referral to this hospital, he developed dyspnoea and chest pain. A lump appeared in the right axilla and the chest radiograph showed a mass at the hilum of the right lung. A biopsy of the mass in the axilla revealed a metastatic deposit of an anaplastic carcinoma which, in places, had an oat cell pattern and evidence of vascular invasion (Fig. 7). The tumour bore no resemblance to the original tumour of 1957, and was considered to have originated from a new primary in the right lung.

The patient was given a course of radiotherapy, but died at home seven weeks after the start of treatment. Although no necropsy was performed, it seems certain that he died of a tumour of the right lung 11 years after the initial lobectomy.

**DISCUSSION**

Giant-cell carcinoma of the lung is usually diagnosed at necropsy after a fairly short illness; the published accounts are summarized in Table I. In many of these cases the interval between the onset of symptoms and death was less than six months even though many patients received radiotherapy. In the two larger series, the average length of the terminal illness was as little as 4.6 and 6.1 months. Two cases are recorded as surviving 10 months, but this seems to be the longest survival in this group of cases. In some cases, secondary deposits of the tumour were treated surgically before the primary was discovered (Hiranandani, Deshpande, Deodhar, and Melgiri, 1966; Thomas, 1962).

Table II summarizes the published cases in which the diagnosis was established from the specimen removed at thoracotomy. The number of cases is small, but, in many of the larger series of surgically treated lung tumours, giant-cell carcinoma is not mentioned as a separate entity. Of the nine cases in the table, adequate follow-up data are only given in

**TABLE I**

INTERVAL SEPARATING ONSET OF SYMPTOMS AND DEATH IN CASES OF GIANT-CELL CARCINOMA OF THE LUNG WITH PRIMARY TUMOUR NOT RESECTED

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Cases</th>
<th>Duration of Illness</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nash and Stout (1958)</td>
<td>1</td>
<td>4 wk-7 mth</td>
<td>One treated with radiation</td>
</tr>
<tr>
<td>Bendel and Ishak (1961)</td>
<td>1</td>
<td>8 wk</td>
<td></td>
</tr>
<tr>
<td>DeAngelis et al (1961)</td>
<td>1</td>
<td>4 mth</td>
<td></td>
</tr>
<tr>
<td>Hellstrom and Fisher (1963)</td>
<td>17</td>
<td>4-6 mth (mean)</td>
<td>Removal of secondary in ileum</td>
</tr>
<tr>
<td>Thomas (1962)</td>
<td>1</td>
<td>8 wk</td>
<td>Radiation in three cases</td>
</tr>
<tr>
<td>Flanagan and Roeckel (1964)</td>
<td>4</td>
<td>7 wk-6 mth</td>
<td></td>
</tr>
<tr>
<td>Friedberg (1965)</td>
<td>2</td>
<td>5 wk and 6 mth</td>
<td></td>
</tr>
<tr>
<td>Guillan and Zelman (1966)</td>
<td>11</td>
<td>3-10 mth</td>
<td>Radiation and chemotherapy</td>
</tr>
<tr>
<td>Herman et al (1966)</td>
<td>63</td>
<td>6-1 mth (mean)</td>
<td>Removal of secondary from jaw</td>
</tr>
<tr>
<td>Hiranandani et al (1966)</td>
<td>1</td>
<td>8 mth</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II**

PUBLISHED CASES OF GIANT-CELL CARCINOMA OF THE LUNG WITH REMOVAL OF PRIMARY TUMOUR

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Cases</th>
<th>Age and Sex</th>
<th>Treatment</th>
<th>Duration of Postoperative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nash and Stout (1958)</td>
<td>1</td>
<td>34M</td>
<td>Lobectomy, tumour arose in a congenital cyst</td>
<td>4 months</td>
</tr>
<tr>
<td>Ozello and Stout (1961)</td>
<td>1</td>
<td>60F</td>
<td>Lobectomy</td>
<td>Alive 6 weeks after operation</td>
</tr>
<tr>
<td>Bendel and Ishak (1961)</td>
<td>1</td>
<td>40M</td>
<td>Pneumonectomy</td>
<td>10 months</td>
</tr>
<tr>
<td>Enjilji (1966)</td>
<td>1</td>
<td>33M</td>
<td>Lobectomy</td>
<td>3 months</td>
</tr>
<tr>
<td>Guillan and Zelman (1966)</td>
<td>1</td>
<td>53M</td>
<td>Lobectomy and radiation</td>
<td>13 months</td>
</tr>
<tr>
<td>Kern et al (1968)</td>
<td>1</td>
<td>57M</td>
<td>Not specified</td>
<td>Alive 8 years after operation</td>
</tr>
<tr>
<td>Weilons et al (1968)</td>
<td>3</td>
<td>---</td>
<td>Not specified</td>
<td>One alive after 1 year; none after 5 months</td>
</tr>
</tbody>
</table>

**TABLE III**

MAIN PATHOLOGICAL FEATURES AND SURVIVAL TIMES OF THREE CASES OF GIANT-CELL CARCINOMA OF THE LUNG TREATED BY Lobectomy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Lymph Nodes</th>
<th>Duration of Postoperative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28M</td>
<td>Left upper lobe</td>
<td>6</td>
<td>Not involved</td>
<td>64 months</td>
</tr>
<tr>
<td>2</td>
<td>71M</td>
<td>Right lower lobe</td>
<td>3</td>
<td>Not involved</td>
<td>13.4 months</td>
</tr>
<tr>
<td>3</td>
<td>56M</td>
<td>Right upper lobe</td>
<td>9 × 7.5</td>
<td>Involved by direct extension</td>
<td>11 years</td>
</tr>
</tbody>
</table>
five. In the case of Ozzello and Stout (1961), the period of observation is too short to be of any value and in the series described by Wellons, Johnson, Benson, Pate, Wilcox, and Peters (1968) the actual survival times are not recorded.

The details of the present three cases are given in Table III; the survival times were six-and-a-half months, 13½ months, and 11 years from the time of operation. If the duration of the preoperative symptoms is added to these figures, all these patients survived for more than a year. When these figures are combined with the data in Table II, the fate of the eight patients whose course is known as follows: two died within six months, two died within 12 months, and two within 18 months, and the remaining two patients survived for longer than eight years. These figures show that, as compared with Table I, the duration of the disease is longer in half of the patients treated by surgery.

Some features of the three present cases deserve special comment. In case 1, the patient was very young and a striking feature was the presence of a thick fibrous capsule (Fig. 3); there was nothing to suggest that this might have been an old tuberculous scar and the patient’s Mantoux reaction was known to be negative. It is possible that this tumour arose in some anomaly of the upper lobe such as a congenital cyst. Such an explanation is supported by one of the patients described as case 4 of the series of Nash and Stout (1958) in which the tumour was thought to have arisen in a congenital cyst; this patient was also young. In the present case, the patient was young and although the lymph nodes were not involved, death occurred six-and-a-half months after operation and a year after the onset of symptoms.

In case 2, the tumour was small and the lymph nodes were not involved but death occurred 13½ months later. In a patient of this age it cannot be assumed that death was due to cancer without confirmation by a necropsy but the radiological appearance of an enlarging mass in the opposite lung make it almost certain that he died as a result of metastases.

Case 3 is particularly interesting because of the long period of survival after removal of what was a very large and extensive tumour which extended as far as the resected margin of the bronchus. This is rather similar to the case of giant-cell carcinoma of the lung which was described by Kern, Jones, and Chapman (1968); in their case the patient was alive eight years after removal of a tumour which also extended to the plane of resection. It is, perhaps, worth noting that in this tumour the cells were more cohesive than in the other two cases (Fig. 6), but it cannot be surmised whether this feature had any connexion with the long period of survival. In case 3, the terminal part of the history and the biopsy make it almost certain that this patient died of a tumour arising in the remnants of the right lung. Although this cannot be proved in the absence of a necropsy report, the presence of a hilar shadow and a deposit of a tumour which was partially of an oat cell pattern strongly suggest that he died of a carcinoma of the lung. This should probably be considered as a second primary rather than a recurrence as the tumours were different in histological appearance and they were widely separated in time. If giant cell carcinoma is as rapidly progressive as Table I suggests, it seems unlikely that the patient could have harboured the original tumour for 11 years.

The epithelial origin of giant-cell carcinoma of the lung was confirmed in one case by Ozzello and Stout (1961) who were able to study the tumour by means of tissue culture. In the WHO classification of lung tumours (Kreyberg, Liebow, and Uehlinger, 1967) giant cell carcinoma of the lung is included in group IV, the large-cell carcinomas. It is described as being composed of large, highly pleomorphic cells with strongly eosinophilic cytoplasm and bizarre often multiple nuclei. All three of the present tumours fit this description. Giant-cell carcinoma of the lung may be distinguished from rhabdomyosarcoma by the absence of cross striations and the occasional presence of epithelial mucin and phagocytosed debris within the tumour cells.

Most authors have regarded giant-cell carcinoma of the lung as an anaplastic variant of adenocarcinoma (Hellstrom and Fisher, 1963; Friedberg, 1965; Herman, Bullock, and Waken, 1966). Some of the tumours described by these authors contained areas suggestive of glandular differentiation and in some the cells contained diastase-resistant, PAS-positive droplets. On the other hand, almost any type of carcinoma of the lung may contain a few giant cells (Walter and Pryce, 1955) so that the mere presence of giant cells cannot be regarded as sufficient for the diagnosis of giant-cell carcinoma. The presence of giant cells can only be regarded as important if they are present in significant numbers and the tumour is otherwise undifferentiated. The presence of PAS-positive droplets and phagocytosis by tumour cells are helpful but not specific features. It is probable that giant-cell carcinoma only differs from the large cell undifferentiated type of tumour in the degree of anaplasia rather than in any absolute sense and it is questionable whether it is legitimate to separate these two entities solely on the basis of the presence of giant cells. The very variable behaviour of the tumour in surgically treated cases, which include survivals ranging from three months to 11 years, may be a further indication that giant-cell carcinoma is not a homogeneous entity.
It is interesting that in case 2 the tumour contained areas of clear cells; clear-cell carcinoma of the lung is regarded as a variant of adenocarcinoma (Morgan and MacKenzie, 1964). Therefore, the coexistence of giant-cell areas and clear-cell areas in the one tumour can be taken as further evidence that giant-cell carcinoma is, in some cases, a highly anaplastic type of adenocarcinoma. This extreme degree of anaplasia is the probable reason for the aggressiveness of this type of cancer but the present cases show that prolonged survival is possible if the tumour can be resected.

I wish to thank Mrs V. Stanisavljevich and Mrs A. Stovall for preparing the histological sections.

REFERENCES