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Metastatic carcinoma of the pleura

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Pleural secondaries are a frequent finding at necropsy in cases of carcinomatosis, and their presence is of such prognostic significance that much effort has been made in the field of diagnostic cytology as applied to the examination of serous effusions (Foot, 1954; Luse and Reagan, 1954a and b; Papanicolaou, 1954; Leuallen and Carr, 1955; Foot, 1956; Myerson, 1956). The relevant literature has been well reviewed by Spriggs (1957), and a less critical view of the investigation is now accepted (Naylor and Schmidt, 1964) than that adopted by Scadding (1955). In recent years special interest has been shown in the cytological diagnosis of pleural mesotheliomas (Klempman, 1962; Manguikian and Prior, 1963; Naylor, 1963) out of all proportion to the incidence of this condition.

The subject of pleural involvement by secondary carcinoma is only briefly mentioned by Spencer (1962), and yet it is of interest since its pathogenesis and the factors influencing the appearance of effusions are poorly understood.

It appeared that a study of necropsy material in this department would be worth while, although cytological material obtained during life was available in only a few of the cases.

METHOD OF STUDY

The histological files of this department contain necropsy material from 52 examples of metastatic carcinoma of the pleura obtained between the years 1960 and 1964 inclusive. In each case the anatomical extent of the pleural metastases, the origin and structure of the tumour, the precise nature of the pleural involvement, and the presence of inflammation and fibrosis were recorded together with alterations of the surface endothelium and changes in adjacent lung parenchyma. The distribution and extent of lymphatic metastases and the presence of hepatic metastases were also noted. Serous effusions were examined during life in 14 cases and the cytological findings were reviewed.

RESULTS

Table I shows the distribution of the primary tumours together with the respective cases showing visceral pleural involvement only, parietal involvement only, and involvement of both layers.

TABLE I

DISTRIBUTION OF CASES IN PRESENT SERIES

Site of Primary Tumour	Pleural Involvement		
	Visceral	Parietal	Visceral and Parietal
Bronchus	3	—	26
Breast	5	—	4
Pancreas	2	—	2
Stomach	4	1	—
Caecum	—	—	1
Gall-bladder	1	—	—
Prostate	—	—	1
Ovary	—	—	1
Unknown	—	—	1
Total ..	15	1	36

Table II shows the distribution of the primary tumours in the cases associated with hepatic metastases. In Table III the cases of bronchial origin are sub-divided into four groups according to the presence of unilateral or bilateral pleural involvement and the presence or absence of hepatic metastases. Table IV shows the distribution of the histological types in the 29 cases of bronchial carcinoma. Various aspects of pleural involvement are illustrated in Figs 1 to 6 and are discussed below.

DISCUSSION

In the present series more than half the examples are of bronchial origin, and the pleural metastases must be accepted as usually arising from pulmonary arterial tumour emboli, a fact of interest since the importance of arterial invasion by bronchial carcinoma has only fairly recently been recognized (Ballantyne, Clagett, and McDonald, 1957; Pryce and Walter, 1960). Although

TABLE II

DISTRIBUTION OF PRIMARY TUMOURS IN CASES ASSOCIATED WITH HEPATIC METASTASES

Site of Primary Tumour	Pleural Involvement		
	Visceral	Parietal	Visceral and Parietal
Bronchus	1	—	12
Breast	5	—	2[2,3]
Pancreas	2	—	2
Stomach	3[1]	1	—
Caecum	—	—	1
Gall-bladder	1	—	—
Prostate	—	—	1
Ovary	—	—	0[4]
Unknown	—	—	1
Total	12	1	19

[1] One case of gastric carcinoma unassociated with hepatic secondaries was an example of retrograde lymphatic spread to the pleura.
[2] One case of mammary carcinoma unassociated with hepatic secondaries was an example of direct neoplastic spread through the chest wall.
[3] Another case of mammary carcinoma similar to that mentioned above.
[4] The single case of ovarian carcinoma was an example of direct neoplastic spread through the diaphragm.

TABLE III

ANALYSIS OF CASES OF BRONCHIAL CARCINOMA IN THE PRESENT SERIES

	Unilateral	Bilateral
Hepatic metastases present	6	6
Liver not involved	14	3[1,2]

[1] One of these cases was an example of retrograde lymphatic spread from infiltrated mediastinal lymphatic nodes.
[2] The second case was an example of alveolar cell carcinoma of multifocal origin; there were no lymphatic metastases present.

TABLE IV

DISTRIBUTION OF CASES OF BRONCHIAL CARCINOMA ACCORDING TO HISTOLOGICAL TYPE

Histological Type	No. of Cases
Oat cell	11
Undifferentiated	5
Epidermoid	5
Squamous	1
Adenocarcinoma	6
Alveolar cell	1

the total number of cases is small, a study of Table IV indicates that this tendency to pulmonary arterial invasion is not the property of a particular histological type, since the proportion of oat-celled carcinomata (11 out of 29 cases) is in accord with the published figures for the incidence of this type in two large series (Bryson and Spencer (1951) 36·0%; Walter and Pryce (1955) 37·1%). A study of the present material showed no evidence that focal pleural secondaries had arisen by lymphatic permeation of the lung parenchyma, except in peripheral tumours and where bronchial carcinomata were accompanied by very extensive parenchymal and centrifugal peribronchial infiltration.

Bilateral pleural involvement by bronchial carcinoma is clearly related to the presence of hepatic metastases, consistent with the occurrence of parenchymal secondaries in the opposite lung. This interpretation of the results shown in Table III is strengthened by the fact that, of the three cases without hepatic involvement, one was an example of retrograde lymphatic spread from infiltrated mediastinal glands (Fig. 1) while another was an example of alveolar cell carcinoma with primary foci in both lungs.

Pleural metastases from other primary sites are usually a manifestation of tertiary spread from established hepatic secondaries, a relationship established in Table II. In only one case of mammary carcinoma was there evidence of direct spread through the chest wall to the parietal pleura, but in two larger series this factor was important (Porter, 1965; Stoll, 1965). The frequency of remote visceral metastases in these cases at necropsy is also an indication that the development of the pleural secondaries is usually a terminal event. There was no significant variation between the histological structure of the primary tumours and that of their pleural secondaries.

The evolution of a pleural metastasis can only be deduced by comparison of individual tumour foci in a number of cases. One of the earliest examples of pleural involvement in which the tumour foci were both small and scanty is shown (Fig. 2) where pleural metastases of gastric origin were clearly the result of pulmonary arterial embolism; the small tumour focus (Fig. 3) had interrupted the normal centrifugal flow of lymph in the subpleural zone causing oedema of an interlobular septum. In the absence of inflammatory reaction the pleural endothelium is often preserved for an appreciable time, as in Fig. 4, where a metastasis, 0·8 cm. in diameter, of bronchial origin shows no significant parenchymal invasion. This occurs invariably in the presence of inflammation; in Fig. 5 a secondary deposit of bronchial origin in the visceral pleura has invaded the parietal layer through a zone of fibrinous exudate. Inflammatory changes adjacent to pleural metastases were found to be variable in intensity and distribution and were frequently absent. When present they were apparently related to pneumonic changes in the adjoining lung parenchyma. The same comments apply to the

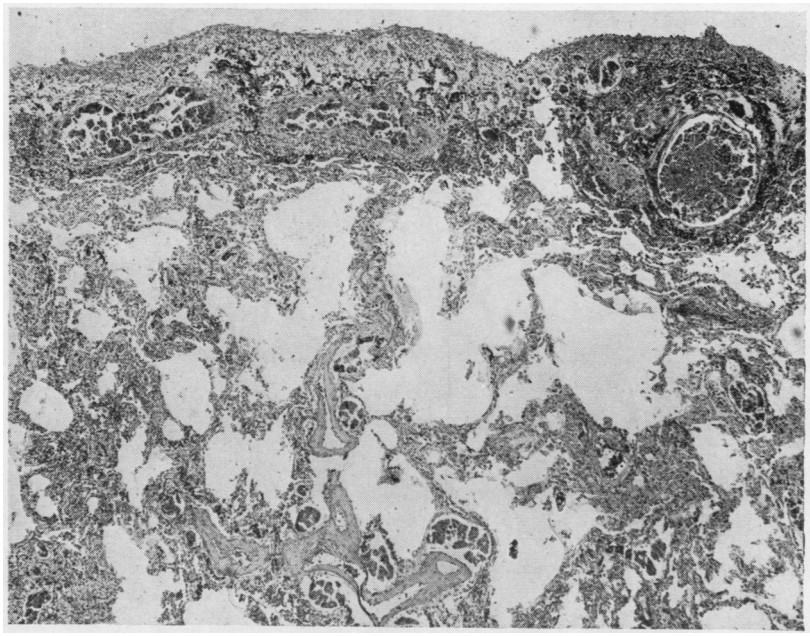

FIG. 1. *Extensive retrograde lymphatic spread of a small bronchial carcinoma from infiltrated mediastinal lymphatic nodes without nodule formation in the visceral pleura. H. and E.,* ×25.

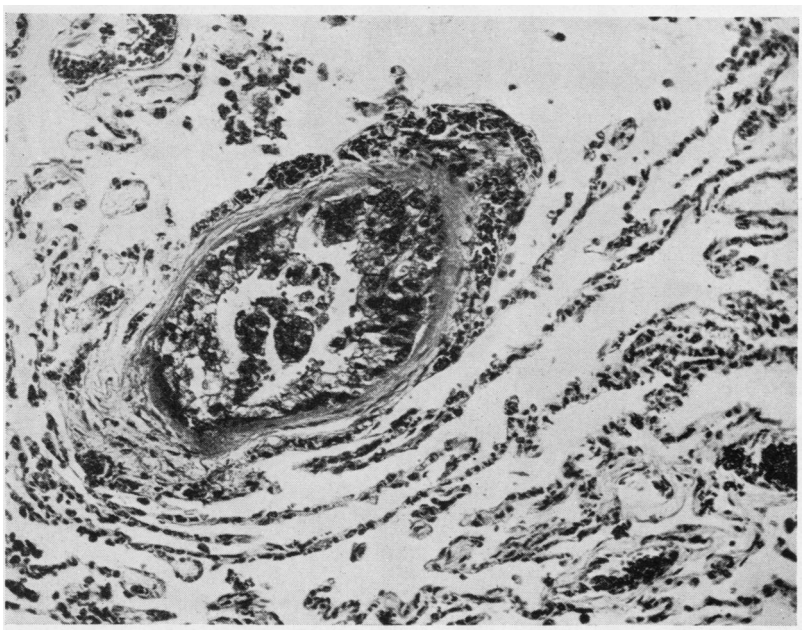

FIG. 2. *Tumour embolus of gastric origin occluding a small pulmonary artery immediately subjacent to the pleura. H. and E.,* ×120.

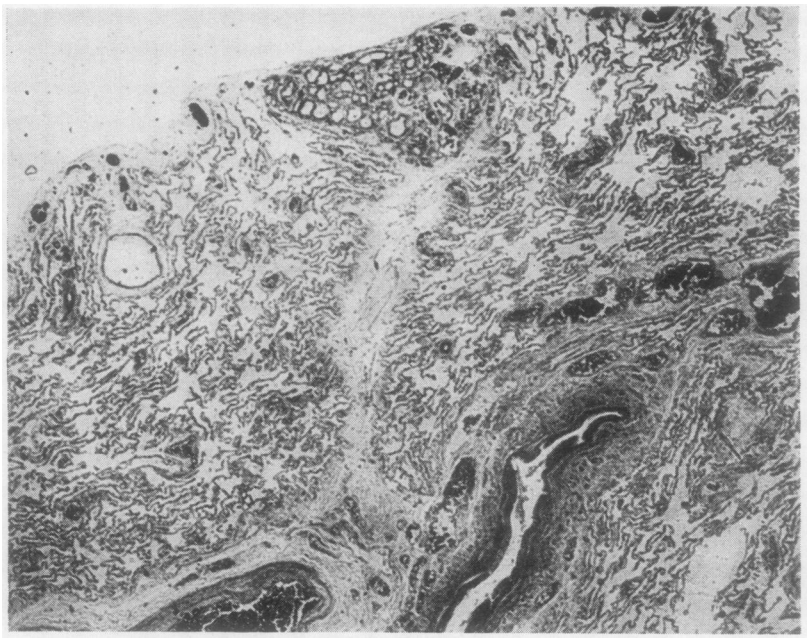

FIG. 3. *Another small tumour embolus, from the same case as shown in Fig. 2, has caused oedema of an interlobular septum by interrupting the normal centrifugal flow of lymph in the subpleural zone. H. and E.,* ×20.

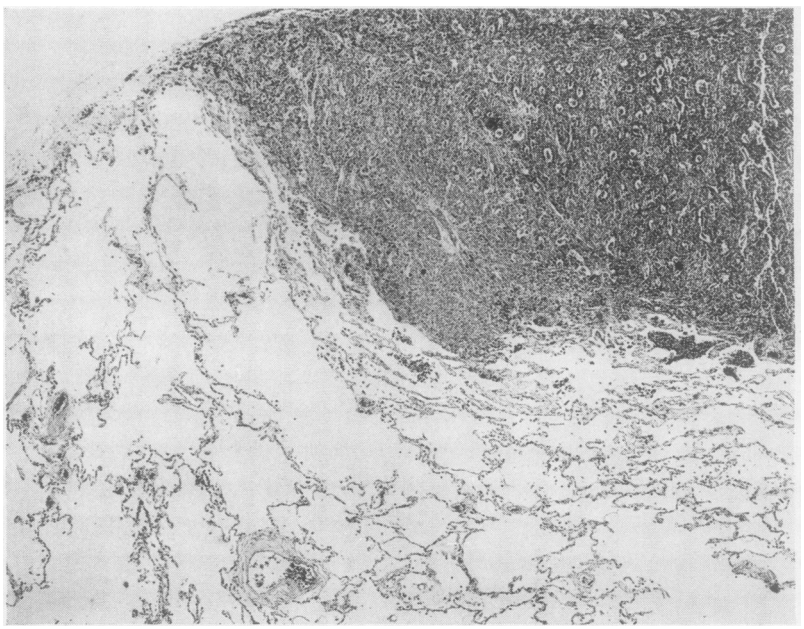

FIG. 4. *A large visceral pleural metastasis of oat-celled bronchial carcinoma shows no significant parenchymal invasion. The deep margin of the infiltrated pleura is still defined by an irregular zone of anthracotic pigmentation. H. and E.,* ×25.

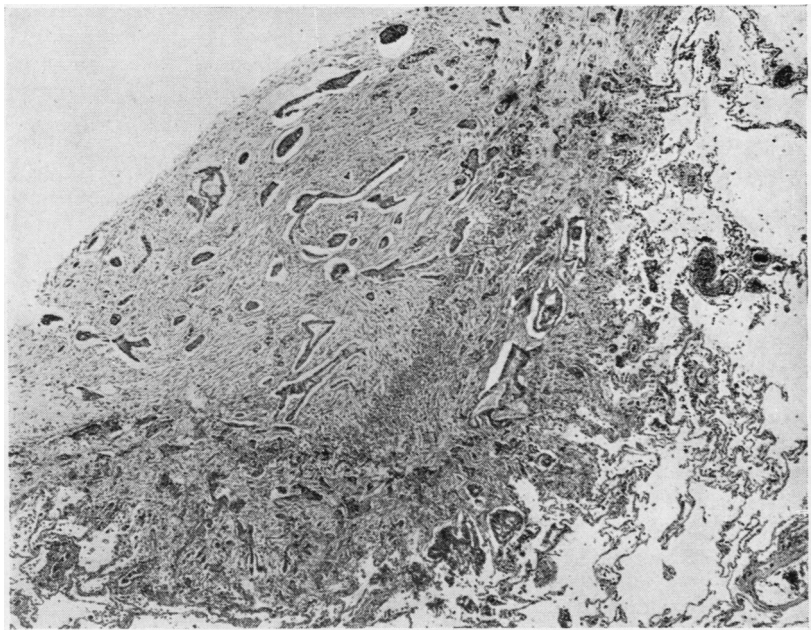

FIG. 5. *A small secondary deposit of bronchial origin in the visceral pleura has spread across a zone of fibrinous exudate. Artefactual stripping of the nodule from the parietal layer occurred at necropsy. H. and E.,* ×27.

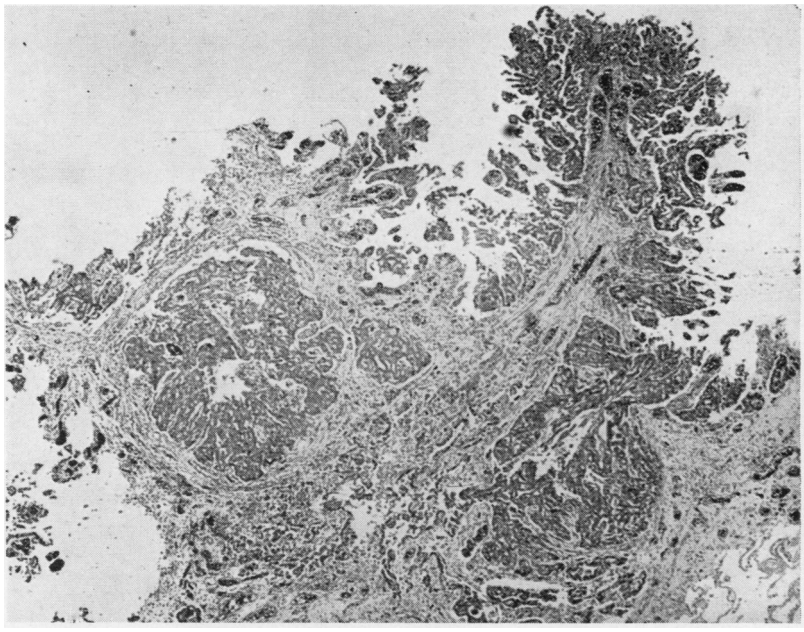

FIG. 6. *A vascular secondary deposit of ovarian origin implanted on the visceral pleura as a result of transdiaphragmatic spread. H. and E.,* ×25.

occurrence of pleural fibrosis, but the presence of preformed fibrous adhesions predisposes to rapid neoplastic spread across the pleural cavity. This occurs regardless of the aetiology of such adhesions.

In the present series the development of a serous effusion was related closely to neoplastic infiltration of mediastinal glands; the extent of pleural involvement by nodular metastases bore no such relationship. The example illustrated (Fig. 1) is of interest in view of the association between massive bilateral effusions and an absence of nodular metastases. These findings are in accord with the view that the fluid outflow from a pleural effusion is via lymphatics (Stewart, 1963); they also explain the fact that pleural effusions do not develop in cases where the pleura is involved by secondary sarcoma because of the usual absence of lymphatic metastases.

A pleural effusion was present in 31 out of 52 cases in the present series, and a grossly haemorrhagic effusion was present in only nine of these. The presence of a haemorrhagic effusion is of great diagnostic importance but the reason for its occurrence was often not clear. In a few cases the source of the haemorrhage was obviously from vascular papillary tumours (Fig. 6), but more often the neoplastic infiltration was restricted to the deeper layer of the pleura where occlusion of small venules occurred; this process resulted in vascular engorgement of the superficial layer and haemorrhage through the endothelial surface in a manner analogous to that occurring in pachymeningitis interna haemorrhagica (Russell and Cairns, 1934). There was no evidence for any inflammatory basis for such haemorrhage, as suggested by Willis (1960), and it was, moreover, of interest that in many cases there had clearly been a substantial time interval between the final occurrence of haemorrhage and death. This was indicated by the fact that many effusions encountered at necropsy were transparent and dark brown due to the presence of abundant degraded blood pigment. It appeared, therefore, that the more gross neoplastic pleural infiltration was often associated with a diminished haemorrhagic tendency.

Although specimens of pleural fluid were examined during life in only 14 cases, some points of interest emerge on review of the cytological findings. Thus a preponderance of endothelial cells occurred in only two cases and in the remainder such cells were scanty or absent. This was reflected by a notable absence of endothelial-cell hyperplasia in the histological material and establishes that the absence of endothelial cells from a pleural fluid is not a differential diagnostic point in favour of tuberculosis, in contrast to the view of Widal and Ravaut (1900). The variable cytological features of pleural effusions associated with bronchial carcinoma and with more distant primary tumours have been emphasized by Hinson (1961) and were confirmed in the present study. Malignant cells were present in 11 out of 14 cases and were often numerous, although in one case only two cells could be identified after prolonged search of a film. The presence of red cells was established microscopically in every case except one, although the effusions were macroscopically free from blood in six cases.

SUMMARY

In an analysis of necropsy material from 52 examples of metastatic carcinoma of the pleura it was found that over half of the cases were of bronchial origin and that the pleural secondaries had arisen from pulmonary arterial tumour emboli. Pleural metastases of bronchial origin occurred relatively early in the course of the disease, whereas in other visceral primary tumours their appearance was a terminal development. Bilateral pleural involvement was related to the presence of hepatic metastases. Pleural secondaries may become large without evidence of parenchymal invasion, but in the presence of inflammation or of preformed fibrous adhesions there is rapid spread across the pleural cavity. Effusions developed as a result of neoplastic infiltration of mediastinal lymph nodes and were not related to the extent of pleural involvement by nodular metastases. There was evidence that the later stages of pleural involvement by secondary carcinoma were often associated with a diminished haemorrhagic tendency.

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