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PLEURAL TUMOURS

BY

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The commonest pleural tumour is a metastasis, and the commonest source of such a metastasis is a primary tumour in the lung. Primary pleural tumours are not only rare but their origin from the pleura is disputed. The purpose of this paper is to outline the clinical behaviour of pleural metastases and to compare this with the natural history of the group of tumours believed to be of pleural or subpleural origin in order to establish that, on clinical grounds, there is justification for distinguishing the latter group from metastases. A further purpose is to draw attention in one group of pleural tumours to the absence of correlation between the histological assessment of malignancy and prognosis.

During a ten-year period when 3,000 patients investigated in the Regional Thoracic Unit in Edinburgh were found to have a bronchial carcinoma, 220 of these were shown at thoracoscopy, thoracotomy, or necropsy to have pleural metastases, as distinct from pleural invasion in continuity with either the primary tumour or mediastinal glandular metastases. The incidence of pleural metastases may well be higher in this series, since a number of patients with extrathoracic extension of tumour were not submitted to either thoracoscopy or thoracotomy and later died at home without necropsy. Of the 220 patients with pleural metastases from bronchial carcinoma 80% had died within six months of the diagnosis having been established, and none survived a year.

In the experience of this unit pleural metastases are common, although relative to bronchial carcinoma much less common, from primary tumours in the breast (27 cases) and in the kidney (10 cases). The number of cases of pleural metastases from breast carcinoma quoted is not a true reflection of the incidence of mammary tumours metastasizing to the pleura, since only those patients severely dyspnoeic because of the rapid recurrence of pleural effusion, and therefore requiring pleural intubation, or those in whom the diagnosis was in doubt and who therefore required thoracoscopy, were referred to this unit. During the period when 3,000 patients with bronchial carcinoma were investigated, 3,500 patients with primary mammary carcinomata were seen in the Department of Radiotherapy in Edinburgh (McWhirter, 1960). Both these figures are thought to represent fairly accurately the incidence of bronchial and mammary carcinoma during this period in this region. The introduction of nitrogen mustard into the pleural space, various forms of hormone therapy, and the ablation of various endocrine glands prolonged survival for as long as two years in some patients with pleural metastases from mammary carcinoma, but most had died within a year of their first being seen in the Thoracic Unit.

Three of the ten patients with pleural metastases from primary renal carcinoma had undergone nephrectomy before they presented with pleural effusions; in the remaining seven, investigation of a pleural effusion established the diagnosis of pleural metastases from an unsuspected renal primary. All died within a year of the diagnosis of pleural metastasis having been established. Examples of metastases in the pleura from osteogenic sarcoma (three cases), uterine adenocarcinoma (three cases), and prostatic carcinoma (two cases), and one example each of metastases from melanoma of the eye, uterine sarcoma, carcinoma of the cervix uteri, ovarian carcinoma, rectal carcinoma, and testicular seminoma, were encountered. All these patients, in common with those with primary tumours in the lung, breast, or kidney, presented with the clinical features of a pleural effusion and without other evidence of dissemination from the primary tumour. All except the two patients with prostatic tumours and the patient with a seminoma were known to have an extrathoracic tumour at the time of investigation of the pleural effusion. Three of 700 patients with a primary tumour in the proximal alimentary tract (Le Roux, 1961) had pleural metastases as distinct from pleural invasion. None of these 17 patients survived a year from

TABLE I

PRIMARY PLEURAL TUMOURS

Case No.	Age	Sex	Symptoms	Radiographic Features: Single Peripheral Opacity	Radiographic Features: Pleural Shadow	Other Significant Features	Treatment	Macroscopic Features of the Pleura	Histology	Survival from Time of Investigation (yr.): Alive	Survival from Time of Investigation (yr.): Dead
1	63	M	Cough, 10 yr.; dyspnoea 4 yr.; joint pains, 1 yr.	+	—	Abnormal radiograph 4 yr. pre-op. Hypertrophic pulmonary osteoarthropathy	Resection of 1,800 g. tumour with ligation of slender avascular pedicle of visceral pleura	Normal	Fibroma	11	—
2	3	M	Cough; loss of weight; dyspnoea and lassitude	+	—	Left chest bulged; gross mediastinal shift to right	Pneumonectomy with resection of tumour	,,	Fibrosarcoma	14	—
3	52	M	None; M.M.R.	+	—	—	Enucleation of tumour from oblique fissure	,,	,,	4	—
4	53	F	Cough	+	—	Abnormal radiograph 9 yr. before	Tumour in oblique fissure; apical lower segment and posterior segment resected	,,	Fibroma	6	—
5	64	F	None; M.M.R.	+	—	—	Tumour in oblique fissure; apical lower segment and posterior segment resected	,,	,,	5	—
6	58	F	Dyspnoea	+	—	W.R. positive	Pneumonectomy	,,	,,	—	Operative death
7	39	F	None; M.M.R.	+	—	—	Tumour 7 cm. in diameter pedicled on apical segment; pedicle 5 mm. in diameter	,,	Fibrosarcoma	13	—
8	52	M	Dyspnoea increasing 4 yr.	—	+	Lumps on parietal pleura seen on radiograph after induction of pneumothorax	Pleurectomy; radiotherapy	Large nodules	Mesothelioma	—	1½
9	42	M	Dyspnoea and pain increasing 3 yr.	—	+	As in Case 8	Thoracoscopy; nitrogen mustard; radiotherapy	,,	,,	—	3
10	56	M	None; M.M.R.	—	+	As in Case 8	Thoracoscopy; radiotherapy	,,	,,	5	—
11	76	M	Dyspnoea increasing over 1 yr.	—	+	—	,,	Small nodules	,,	5	—
12	58	M	Dyspnoea increasing 1 yr.	—	+	—	Thoracoscopy; pleurectomy; radiotherapy; mustine	,,	,,	—	3
13	66	M	Increasing dyspnoea 1 yr.	—	+	—	Pleuropneumonectomy	,,	Mesothelioma or fibrosarcoma	1	—
14	58	M	Increasing dyspnoea 2 yr.	—	+	—	Pleurectomy	Thick pleura devoid of nodules	Mesothelioma	1	—
15	46	M	Dyspnoea and pain increasing over 2 yr.	—	+	Frozen chest	Pleuropneumonectomy; radiotherapy	Obliterated pleural space	,,	—	4
16	65	M	Dyspnoea and pain increasing over 1 yr.	—	+	Frozen chest	Pleurectomy	,, ,,	,,	—	Postoperative death

the time of investigation of the pleural lesion. The appearances at thoracoscopy in many of the patients found to have pleural metastases were similar to those found in patients referred to later in this paper as having large nodular mesothelioma. In none was the appearance at thoracoscopy similar to that found in the small nodular mesothelioma, and in none was the pleural space obliterated.

During the same ten-year period 16 patients investigated in this unit have been found to have tumours which have been called primary pleural tumours. In nine of these patients the radiographic abnormality was a pleural shadow suggestive of a pleural effusion, and in all these the diagnosis of pleural mesothelioma was made on histological grounds, with the diagnosis of fibrosarcoma offered as an alternative in one. In the remaining seven patients the radiographic abnormality was a single well-circumscribed peripheral opacity; in three of these the diagnosis of fibrosarcoma was made, and in four of fibroma. Details relating to these 16 patients are shown in Table I.

Case Reports

Case 1 (Figs. 1 and 2) is similar to many reported examples of pleural fibroma (e.g., Thomas and Drew, 1953), and it is the only example in the present series of a patient with hypertrophic pulmonary osteoarthropathy. The diagnosis of fibroma was made pre-operatively on the basis of the changes in the joints; joint pain had disappeared by the time the patient was able intelligently to answer questions on the evening of the day of operation, and his fingers were normal three months later. This patient had been found to have an abnormal chest radiograph four years before thoracotomy. At thoracotomy the tumour was found to be attached by a slender avascular pedicle to the apical segment of the left lower lobe.

Case 2 (Fig. 3) is unusual because of the age of the boy (he was 3 years old at the time of thoracotomy) and the size of the tumour, which occupied the left hemithorax and encroached on the right. A confident histological diagnosis of fibrosarcoma was made, and the boy is well 14 years later. In Case 3 (Fig. 4) the unusual feature was the macroscopic appearance of the tumour, which lay in the oblique fissure between middle and lower lobes. The tumour shelled out of the fissure without the sacrifice of any pulmonary tissue, and during manipulation it disintegrated into six small spherical lumps, each well circumscribed and free from its neighbour, the largest the size of a golf-ball and the smallest the size of a pea. The appearance was likened at the time of resection to a nest containing eggs of different sizes. Each separate tumour had the same histological features, called sclerosing fibrosarcoma.

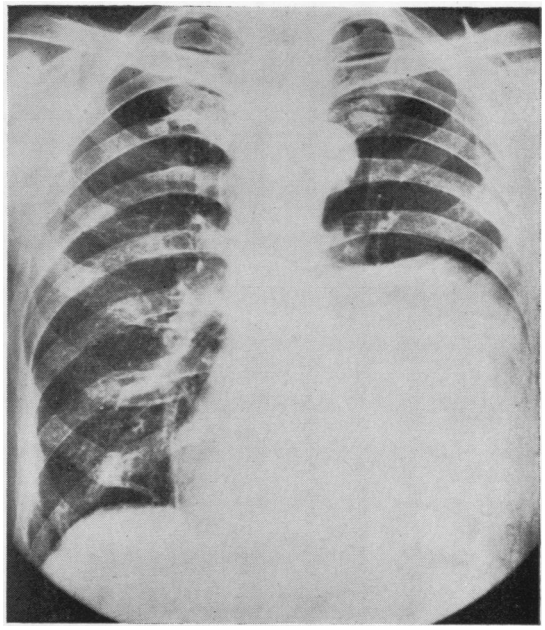

FIG. 1

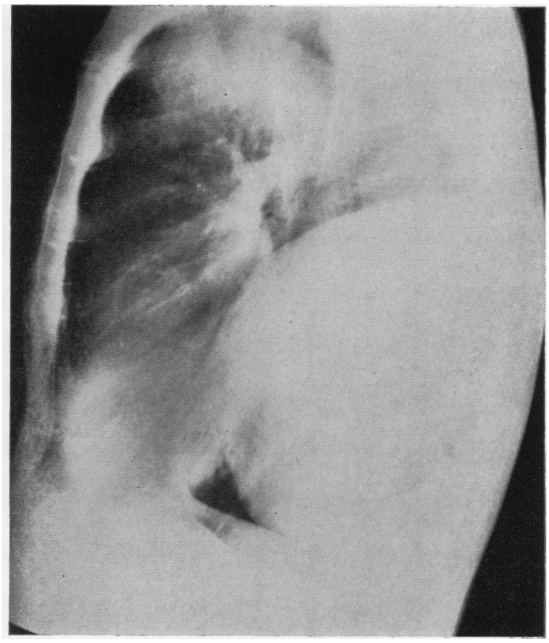

FIG. 2

FIGS. 1 and 2.—Case 1. P.A. and lateral views showing a large intrathoracic fibroma in a patient with hypertrophic pulmonary osteoarthropathy.

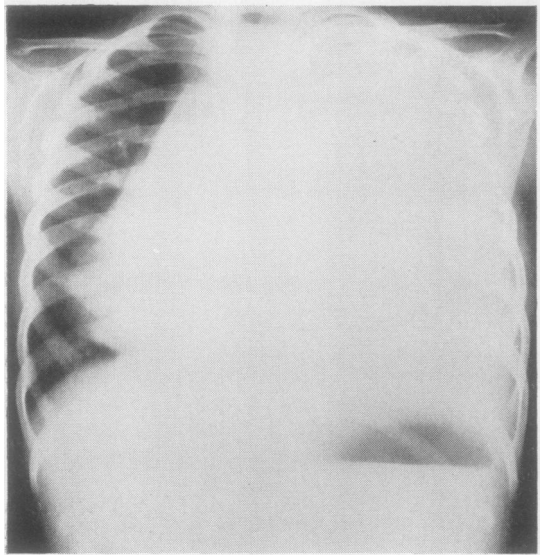

FIG. 3.—Case 2. A large left intrathoracic fibrosarcoma displacing the mediastinum to the right in a boy of 3 years.

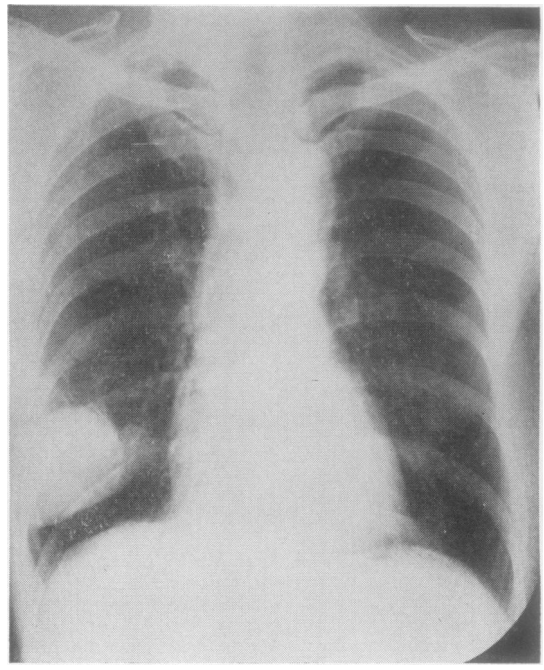

FIG. 4.—Case 3. A " nest " of fibrosarcomata in the oblique fissure.

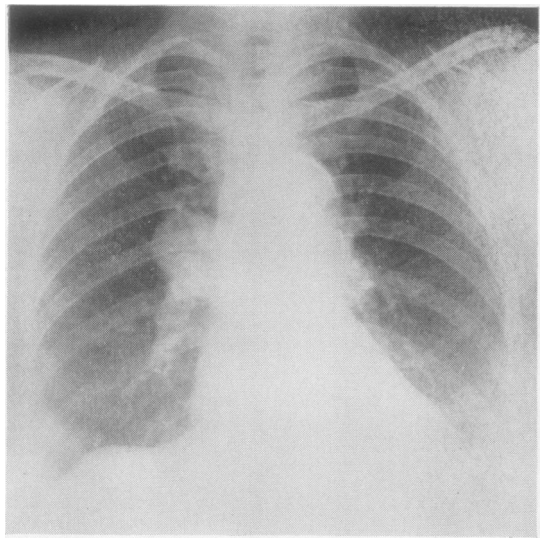

FIG. 5

FIGS. 5 and 6.—Case 4. A P.A. view and a tomogram of a fibroma in the oblique fissure.

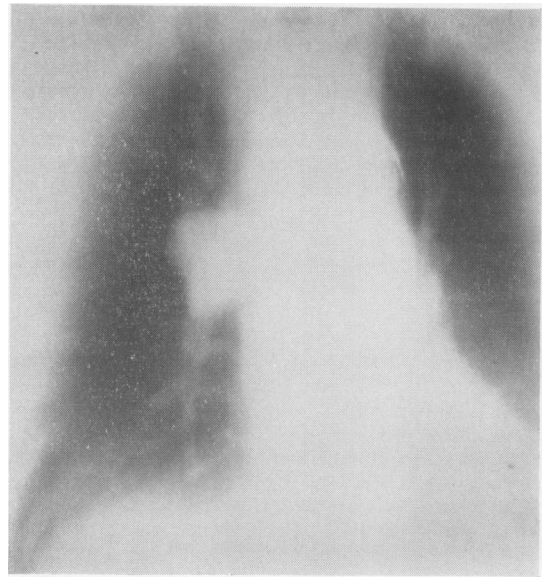

FIG. 6

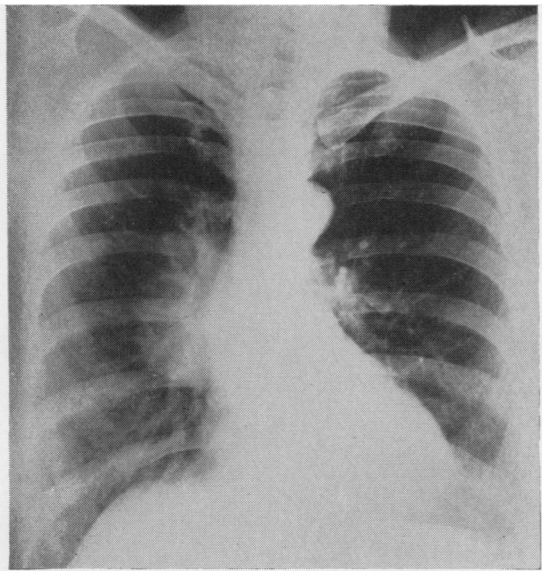

FIG. 7.—Case 5. Another example of a fibroma in the oblique fissure.

Case 4 (Figs. 5 and 6) and Case 5 (Fig. 7) were similar. In each at thoracotomy a lump lay buried in the oblique fissure between the apical segment of the right lower lobe and the posterior segment of the upper lobe, and in each these segments were resected with the lump. Dissection of the operative specimen showed a tumour in the fissure displacing but not invading lung. In neither was the fissure well developed, and in each resection was undertaken in the belief that the tumour was pulmonary and probably an adenoma. In both resection was conservative because of a limited respiratory reserve; a less conservative resection would have meant pneumonectomy. Case 6 is one of the two operative deaths in this series. Thoracotomy was undertaken because of a lobulated opacity 7 cm. in diameter in the periphery of the right lung, without pre-operative lead to the diagnosis. Haemorrhage from the azygos vein contributed to death. The fibroma was described as subpleural in origin, compressing but not invading the subtended lung. The operative findings in Case 7 were similar to those in Case 1, and this is another example of long survival following resection of a tumour called by the examining pathologist a fibrosarcoma.

Case 8 (Fig. 8) and Case 9 (Fig. 9) are examples of pleural mesotheliomata visible on plain films of the chest as large parietal pleural nodules after replacement of a pleural effusion with air. The nodules were all larger than a centimetre in diameter and, in comparison with the small nodular mesothelioma, relatively few in number and scattered over a relatively limited area; the nodules were confined to the parietal pleura in these two examples, and the pleural surface of the nodules was ulcerated. This macro-

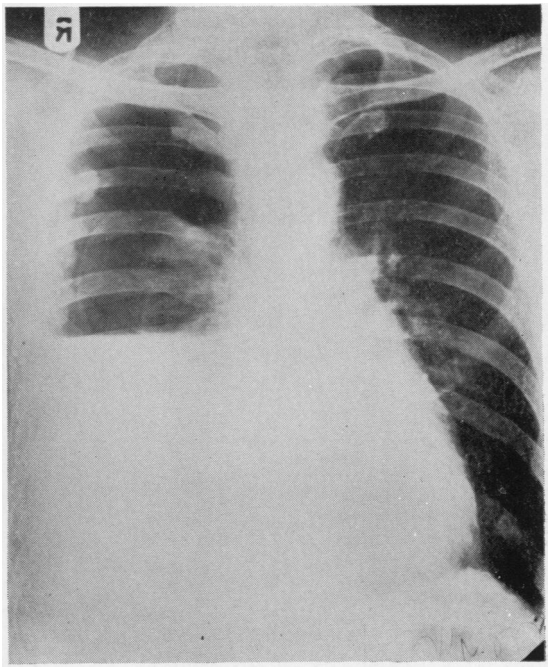

FIG. 8

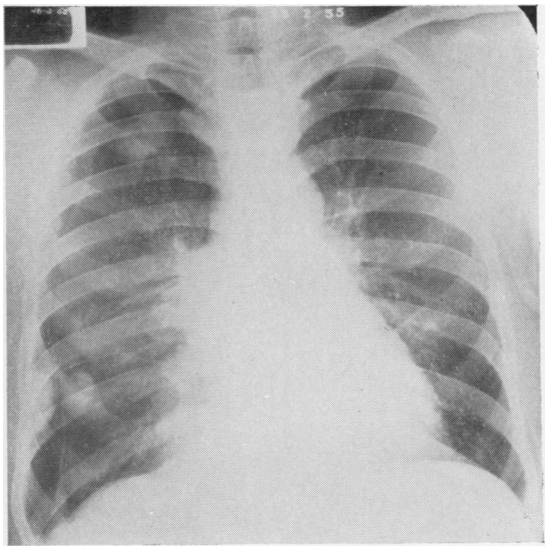

FIG. 9

FIGS. 8 and 9.—Cases 8 and 9. Two examples of large nodular mesotheliomata visible on the parietal pleura after replacement of a pleural effusion with air.

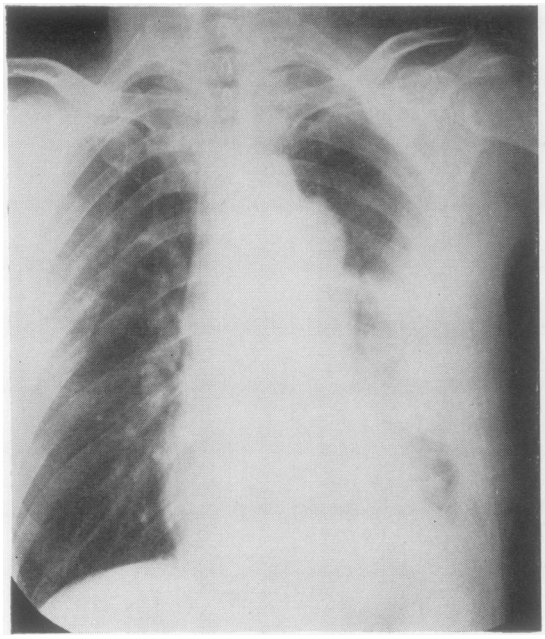

FIG. 10

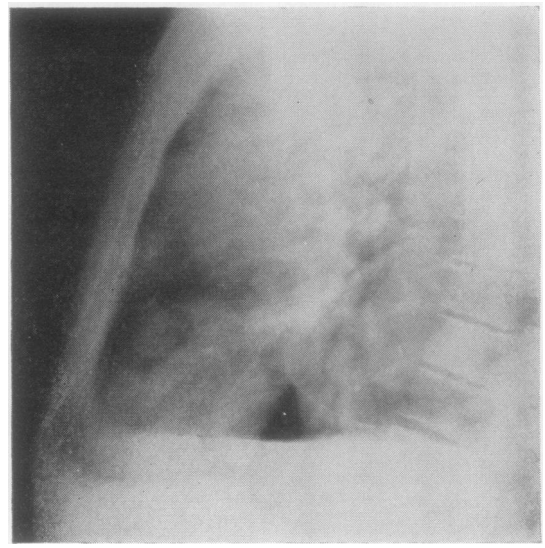

FIG. 11

FIGS. 10 and 11.—Case 10. P.A. and lateral views showing a large nodular mesothelioma visible after the aspiration of pleural liquid without a pneumothorax.

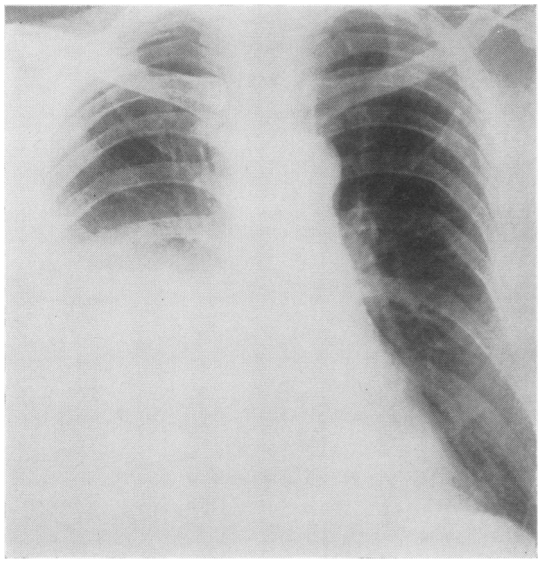

FIG. 12*a*

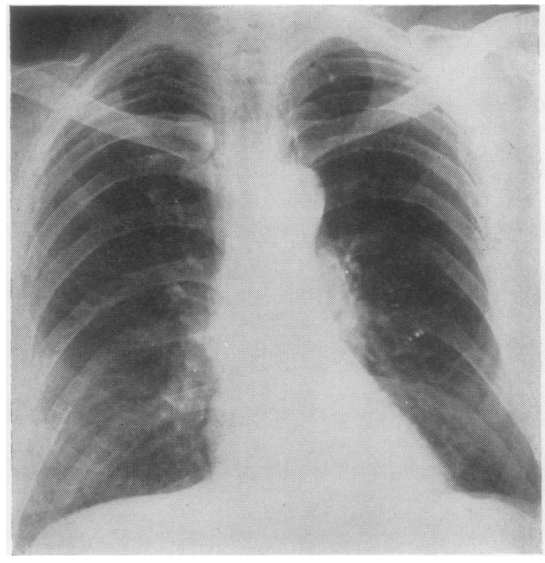

FIG. 12*b*

FIG. 12.—Case 12. P.A. views of the chest (*a*) before and (*b*) after the aspiration of pleural liquid in a patient with a small nodular mesothelioma.

scopic appearance is indistinguishable from that of pleural metastases from any of the sources mentioned earlier. The large nodules on the parietal pleura in Case 10 were visible on plain films after thoracentesis in the absence of a pneumothorax (Figs. 10 and 11). In Cases 8 and 9 death from progress of disease occurred more than five years after the onset of symptoms, and in one case hepatic metastases were found at necropsy. Case 10 is unusual in that the patient presented because of an abnormal mass radiograph; he is well five years after investigation, with certainly no increase in the size of the opacities and possibly a little shrinkage of the lesions radiographically after radiotherapy.

Cases 11, 12, and 13 are examples of patients presenting with pleural effusions and found to have multiple, small, smooth, non-ulcerating parietal pleural tumours, all roughly the same size, none larger than 3 or 4 mm., scattered thickly over the pleural surface, with involvement of the diaphragmatic and mediastinal pleurae but with very little involvement of the visceral pleura. The chest radiographs from Case 12 before (Fig. 12*a*) and after (Fig. 12*b*) aspiration of the effusion are typical of these three cases; the film made after thoracentesis would pass as normal. This patient died three years after pleurectomy, from recurrence of tumour and from metastases. A year before death, pain in the back prompted further radiographic studies and vertebral destruction was seen. At necropsy extensive recurrence of tumour in the pleural space and hepatic and vertebral metastases were found. The histological appearances of the metastases were similar to those of the original operative specimen. Long survival from the onset of symptoms (e.g., Case 11, this patient now being 81 years old) is one feature which distinguishes this group of pleural tumours from pleural metastases. The examining pathologists were unable to decide whether Case 13 was an example of pleural mesothelioma or fibrosarcoma.

In Case 14 the parietal pleura was 1 cm. thick but devoid of nodules. The last two patients (Cases 15 and 16) both presented with pain in the chest and dyspnoea; in each the hemithorax was immobile and shrunken, and there was a dense pleural shadow with an obliterated pleural space. In Case 15 the diagnosis of mesothelioma was made from the histological examination of a nodule removed with the scalene pad; the nodule was adjacent to, but not invading, a lymph gland. This patient died four years after pleuropneumonectomy, undertaken because of pain despite the evidence of extrathoracic extension of tumour; at necropsy the hemithorax on the side of pneumonectomy was filled with tumour and the heart was encased in a mass of intrapericardial tumour, death being directly related to cardiac constriction. This patient survived six years from the onset of symptoms and four years from the demonstration of extrathoracic extension of tumour. Case 16, the other operative death, demonstrates the hazard of an extensive pleural resection, with concomitant air leaks from the lung, in a patient with a limited respiratory reserve; multiple persisting fistulae contributed to this patient's death on the eighth post-operative day from respiratory insufficiency.

Of these 16 patients, therefore, seven had a single peripheral spherical radiographic opacity; six of these seven are alive four to 14 years after operation, and one died from operation (from haemorrhage unrelated to the tumour); the histological diagnosis in three of the six survivors was fibrosarcoma; and none has evidence of tumour recurrence. In nine of the 16 patients the radiographic abnormality was a pleural shadow—an effusion in seven and thickened pleura with an obliterated pleural space in two. In these nine patients the pleura was diffusely tumorous, least diffusely where the nodules of tumour were largest, and the histological diagnosis of mesothelioma was offered in all of them, with fibrosarcoma as an alternative in one (with small nodules). In two patients the diagnosis of mesothelioma was qualified by the descriptive term papillary, in two others mucus-secreting, and in one each cuboidal, pleomorphic, and solid. In two mesothelioma was unqualified. Wide variation in the histological structure of diffuse malignant pleural mesothelioma is well recognized. Five of these nine patients have died, one in relation to operation and four one to four years after operation but four to six years after the onset of symptoms. Four are alive, two of these five years after investigation. Extrathoracic metastases were found in one patient during investigation and in two others at necropsy. Long survival is therefore a feature of most of these patients, in comparison with short survival of patients with metastatic tumours in the pleura.

Discussion

Klemperer and Rabin (1931) distinguished two groups of primary pleural tumours, a fibromatous group which they believed had their origin from the tissues deep to the superficial lining cells of the pleura, and a group called mesothelioma, which arose from the surface lining cells of the pleura. Clagett, McDonald, and Schmidt (1952) recognized these two groups of tumours, distinguishable by the circumscription of the one and the diffuseness of the other; they believed that these two groups of tumours had nothing in common except their supposed origin from the pleura, but since both must have a mesothelial origin, they subscribed to and acknowledged the value of the terms "localized fibrous" and "diffuse malignant" mesothelioma. That the

localized fibrous mesothelioma, for which synonymous terms are pleural fibroma, intrathoracic fibroma, and benign localized mesothelioma, is often malignant is clear from the reports in the literature of recurrence of these tumours after resection and their development of invasive properties. Kerr and Nohl (1961) report six examples of recurrence of localized fibrous tumours previously called benign, and Clagett *et al.* (1952) and Ehrenhaft, Sensenig, and Lawrence (1960) also report examples of recurrence after resection of pleural fibromata. All these authors comment on the histological similarity between the original tumour and the recurrence. The rather sweeping generalization that fibroma is the diagnosis of the intellectually destitute was gleaned when one was an undergraduate. The source of this aphorism is forgotten, but its message is valid—every fibroma is a potential fibrosarcoma.

The localized tumours, comprising the first seven cases in this series, cannot therefore be called benign tumours, but their behaviour makes them relatively benign. The diagnosis of fibroma or fibrosarcoma in this type of tumour depends more on the histologist than on the histology. The localized fibrous mesothelioma may have histological features which necessitate calling it a sarcoma, and resection may yet allow of long survival without recurrence, or may have histological features which suggest benignity and resection may be followed by recurrence. Temple and Jones (1954) emphasize that the difference between the highly cellular anaplastic fibrosarcoma and the densely fibrous and apparently benign growth is one only of degree. In one of the nine diffuse tumours called mesothelioma the diagnosis of fibrosarcoma was suggested as an alternative. This implies an overlap between the two groups. This overlap has been emphasized by McCaughey (1958) and by Kahn, Glay, and Madore (1959). If in fact the " pleural " fibroma arises from subpleural tissues and the mesothelioma from the layer of serosal cells comprising the pleural membrane, then such an overlap is acceptable on embryological grounds; the coelomic epithelium and the underlying mesenchyme are both derived from mesoderm and are not separated by a basement membrane. The view of Stout and Murray (1942) that intrathoracic fibroma is a localized form of pleural mesothelioma is widely accepted in the North American literature, and the application of the term mesothelioma to the localized fibrous growth emphasizes its potential malignancy. The behaviour of the diffuse mesothelioma is that of a slow-growing malignant tumour, the course of which is little influenced by any surgical procedure, and claims of prolongation of life by surgical removal of these tumours must be judged with the knowledge that long survival is common in the absence of surgical intervention. The value of resection of mesotheliomata seems purely palliative, achieving palliation in one of three ways—by limiting the reaccumulation of pleural liquid, by relieving pain, or, when accompanied by pulmonary resection, by providing space in which the tumour may pursue its growth for a longer period with less interference with vital structures. The pain produced by diffuse mesothelioma is constant and gnawing in character, suggestive of nerve involvement rather than pleural irritation. Barrett and Elkington (1938) reported examples of pleural mesothelioma with neurological abnormalities—paralysis and sensory loss in the distribution of intercostal nerves on the side of the tumour—and suggested that nerves were involved by the tumour posteriorly, where the anterior primary ramus lies in direct relation to parietal pleura, unprotected by rib.

Willis (1953) denies the existence of mesotheliomata as an entity, but whatever doubts there may be on histological grounds, the clinical behaviour of this group of tumours is different from that of pleural metastases, and long survival of many patients with mesotheliomata is the distinguishing feature.

For simplicity it seems justifiable to attribute to the pleura only one tumour, and that is malignant, a sarcoma. This tumour behaves in one of two ways, with an overlap between these two modes of behaviour: (1) When it is single and localized it usually, but not always, arises in relation to the visceral pleura. It is often associated with the clinical syndrome of hypertrophic pulmonary osteoarthropathy (Thomas and Drew, 1953) and with episodes of chills and fever (Ehrenhaft *et al.*, 1960). The histological features are often those of fibrous tissue only, and yet recurrence of these tumours after resection is not uncommon. (2) When the sarcoma has a more diffuse origin from the pleura it is usually most widely disseminated in relation to the parietal pleura, presents because it produces dyspnoea from pleural effusion, and sometimes pain, has a variable histological pattern sometimes indistinguishable from the first group, and is frequently associated with long survival despite its more clearly definable malignant clinical and histological characteristics. The clinical behaviour of both groups merges, but is clearly different from that of pleural metastases from other malignant tumours.

SUMMARY

The clinical behaviour of pleural metastases, based on 274 cases, is outlined and compared with the behaviour in 16 cases of tumours believed to be primarily pleural. It is suggested that the only primary pleural tumour is a sarcoma, which may be circumscribed or may involve the pleura diffusely. Typical examples of these two varieties of sarcoma behave in a recognizable way which serves to distinguish them, but there is considerable overlap histologically. Pleural sarcoma is a slow-growing tumour associated with long survival, and differs from metastatic pleural tumours which usually result in death within a year.

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