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Benign Pleural Lesions and Malignant Mesothelioma

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Summary. In a series of eighteen diffuse malignant mesotheliomas, five cases were encountered in which thoracic surgery with benign nontumorous diagnosis preceded the development of a malignant mesothelioma by several years. The morphological findings in three of these five cases are compared with the morphology of the tumor specimens and an attempt is made to recognize the earliest possible malignant features. Crowding of mesothelial cells, their variability in size and nuclear hyperchromatism are pointed out as warning signs.

In relation to these findings, the histogenetic significance of predominantly fibroproliferative versus epithelial-like pleural lesions is discussed. A histogenetic classification, based on the studies of eighteen diffuse malignant mesotheliomas, two benign fibrous mesotheliomas, one pleural fibrosarcoma, and numerous pleural plaques as well as reactive mesothelial lesions, is offered. The therapeutic aspects are mentioned.

Key words: Mesothelioma, benign and malignant – Morphology and classification – Premalignant features.

Introduction

The incidence of mesothelial tumors has increased within recent years. This is reflected in the growing amount of related literature (Butchart et al., Elmes et al., Embleton et al., Kovarik; Kucuksu et al., Milne, Putoni et al., Selikoff, Shearin et al., Taryle et al.) as shown, for example, from 1976. It means that more physicians are confronted with the difficult task of how to diagnose a mesothelioma. Since it is a rapidly progressing tumor with unsuccessful treatment, the earliest possible diagnosis is mandatory (Butchart et al., 1976; Schlienger et al., 1969).

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Table 1. Mesothelioma clinical histories

Case	Occupation	I. Surgery	Diagnosis	Histol. type	Follow-up	Med hist.
1. 49 man	Lawyer	12/1953 Pleurodesis: inflammatory adhesions	1/1957 Thoracotomy: mesothelioma	E	Died 1964 no autopsy	Smoker pneumonias
2. 58 man	Salesman	5/1972 Rt. middle lobe resection: pneumonitis and bronchial cyst	9/1972 Explor. laparotomy: mesothelioma	E	Died 1972 autopsy	Smoker
3. 53 man	Machinist	5/1973 Pleural stripping: chron, pleuritis and mesothelial hyparplasia	7/1975 Mediastinoscopy and explor. laparotomy: mesothelioma	E	Died 1975 no autopsy	Smoker Pneumonias
4. 40 man	Sandblaster, painter	1972 Unknown means: atypical TB	3/1974 Rt. upper lobectomy: mesothelioma	S	Died 1975 autopsy	Smoker asbestos exposure TB
5. 31 man	Pilot	4/1972 Pleurodesis: fibrosis and mesothelial proliferation	1/1974 Thoracotomy mesothelioma	S	Alive 5/1975	Pneumonias

For this purpose, we have reviewed the medical histories and the tissue samples from five patients out of eighteen malignant mesotheliomas. These patients had thoracic surgery one to three years prior to the diagnosis of mesothelioma and a benign diagnosis was made on their original tissue, removed at surgery and examined microscopically.

Material and Methods

The available clinical records of these five patients were reviewed. The histological sections from the first surgical biopsies were re-examined in three cases. The results were compared with the clinical and later morphological findings in the five patients and in our series of eighteen diffuse malignant mesotheliomas, two benign fibrous mesotheliomas, one pleural fibrosarcoma, numerous pleural plaques and reactive mesothelial lesions, as they occurred in routine pathology practice. The material was from the surgical procedures as well as from the autopsies in cases where an autopsy was performed.

All tissues were routinely processed and stained with hematoxylin and eosin. Some of the tumors and few of the reactive lesions were stained by special stains; namely, Movat's pentachrome, Masson's trichrome, alcian blue, Meyer's mucicarmin and Gomori's reticulum. Several samples from the tumorous and nontumorous specimens were examined by electronmicroscopy and the printed electronmicrographs were also reviewed.

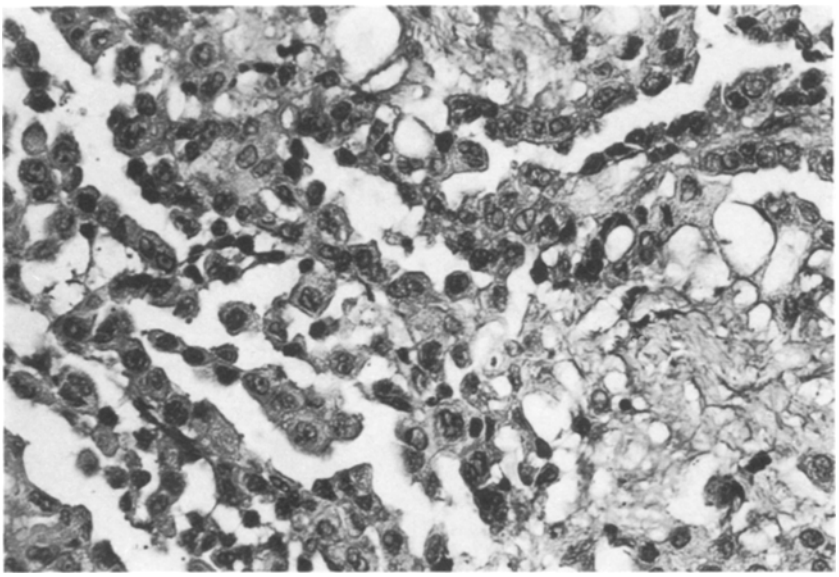


Fig. 1. Case 1: Epithelial type of mesothelioma showing irregular and ill-defined spaces lined by abnormal mesothelial cells. H & E ×420

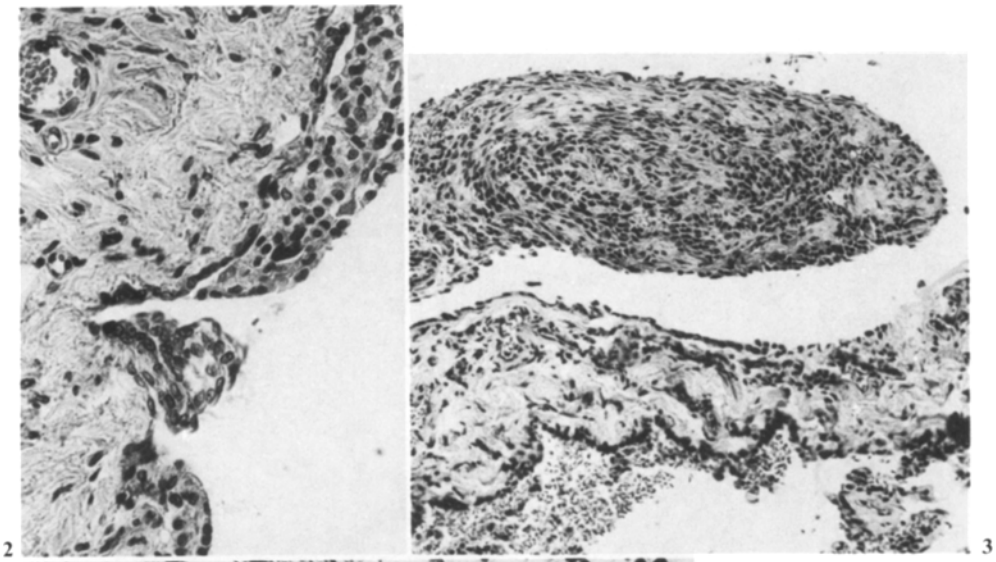
Results

Table 1 summarizes the clinical and morphologic findings of the five patients. Only one had an obvious occupational history of asbestos exposure; four patients were smokers; four of the patients underwent thoracotomy and usually a substantial portion of tissue was submitted for microscopic study. In Case 4, the old records were not available and we obtained information that a former pleural biopsy showed "atypical tuberculosis".

The pleural tissue from the original surgery in Cases 2, 3 and 5 revealed changes from simple mesothelial prominence to extensive inflammatory reaction (Figs. 2, 3, 5, 6, 9, 10). In Case 5, several areas of small spaces lined by uniform cuboidal mesothelial cells were present (Fig. 9). All samples contained small foci of accumulated mesothelial cells either on the surface or in the organizing inflammatory exudate (Figs. 2, 3, 5, 6]. Neither of the microscopic sections was suggestive of a neoplastic lesion. Only by a careful study of more than one tissue block could a few atypical mesothelial cells be identified. The cells were large, of variable sizes, and exhibited nuclear hyperchromasia (Figs. 5, 6, 9).

These five patients developed chest pain and they returned to the hospital. Patients 1, 4 and 5 also experienced an increasing shortness of breath. Patients 2 and 3 developed abdominal masses, pleural and peritoneal effusions.

The ensuing surgical and pathological examination revealed the presence of the spreading pleural tumor and eventually peritoneal extension. In all cases, the tissue was soft, pink and nodular. Histologically, it was recognized as



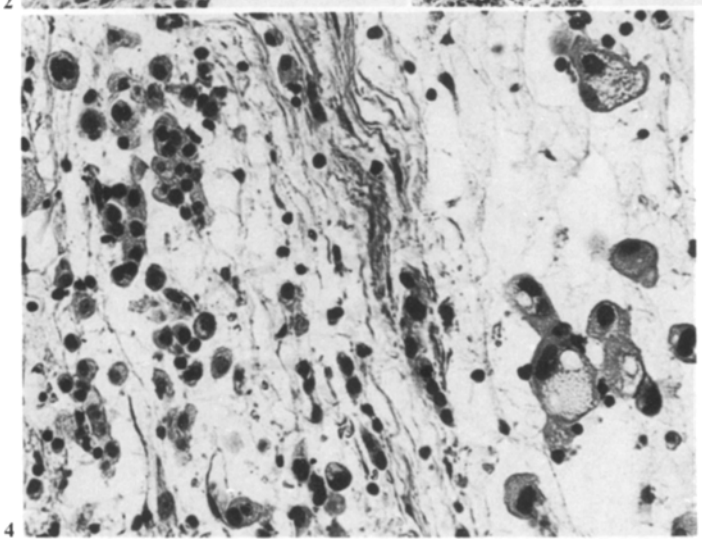


Fig. 2. Case 2: Mesothelial cell proliferation and piling of mesothelial cells on the surface of thickened pleura. H & E ×250

Fig. 3. Case 2: Inflammatory changes and fibrous adhesions of the pleura. The true nature of the cells in the cellular areas is difficult to recognize. H & E ×100

Fig. 4. Case 2: Epithelial type of mesothelioma. The tumorous cells are scattered in loose connective tissue. The cells are large and variable in size, with sharp borders and vacuolated cytoplasm. H & E ×380

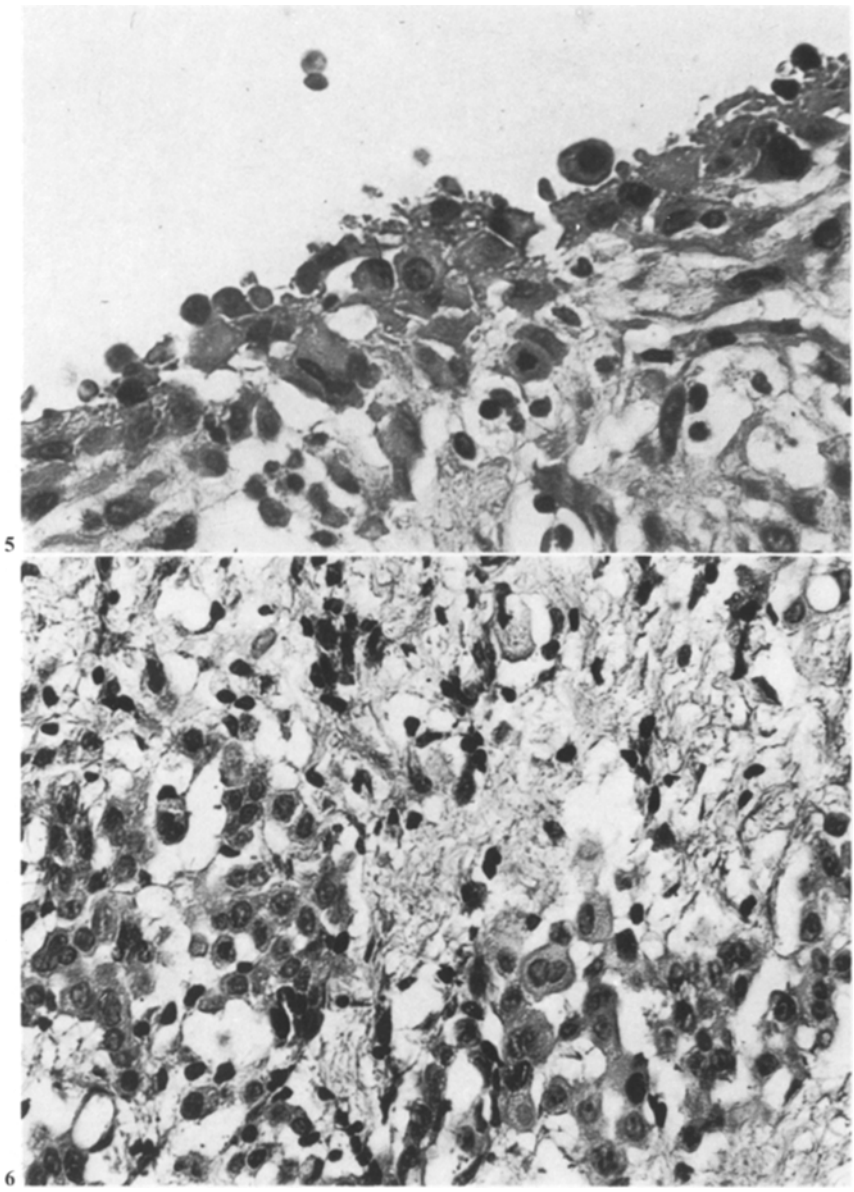


Fig. 5. Case 3: Pleural surface showing pleomorphic mesothelial cells proliferation. H & E ×500

Fig. 6. Case 2: Abnormal proliferating mesothelial cells embedded in fibrous tissue in chronic pleuritis. Note the binucleated cells. H & E ×500

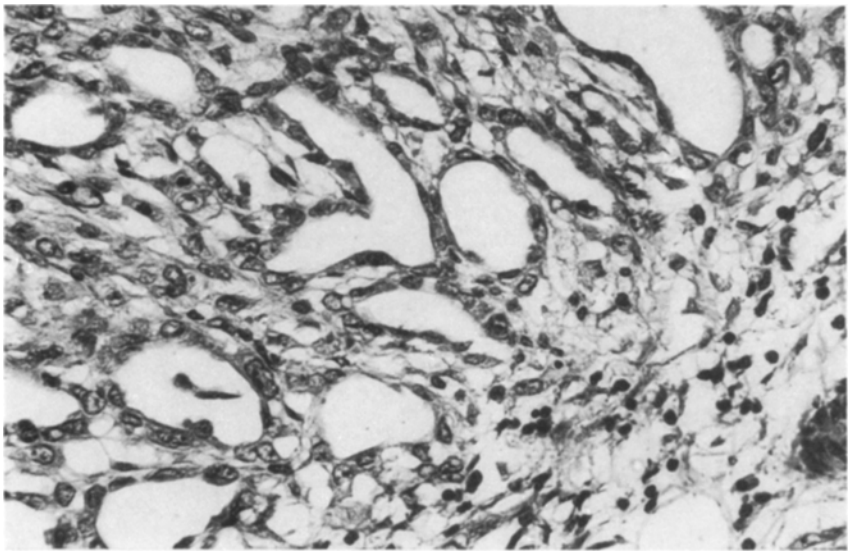


Fig. 7. Case 3: Epithelial type of mesothelioma. The mesothelial cells are uniform, arranged in a reticular pattern with scant loose stroma. H & E ×300

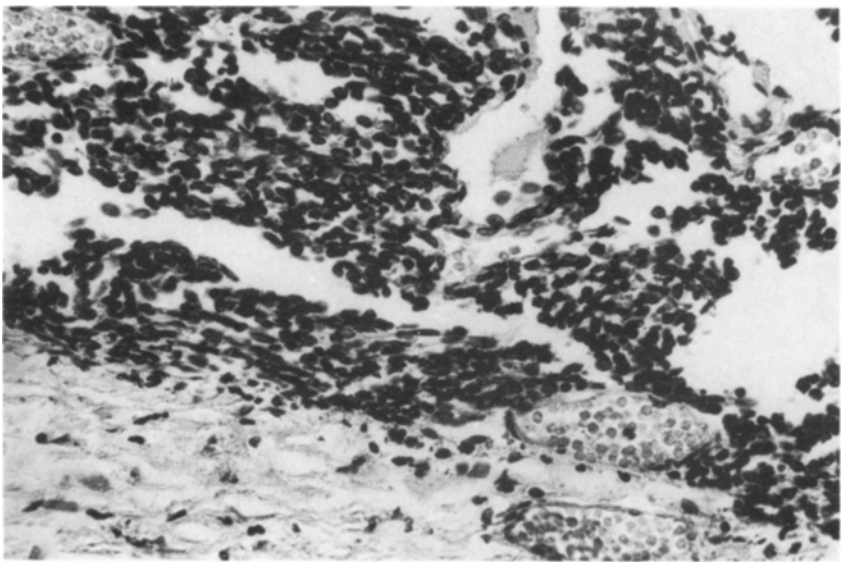


Fig. 8. Case 4: Sarcomatous type of mesothelioma. The tumor forms masses of closely packed small cells with hyperchromatic nuclei. H & E ×300

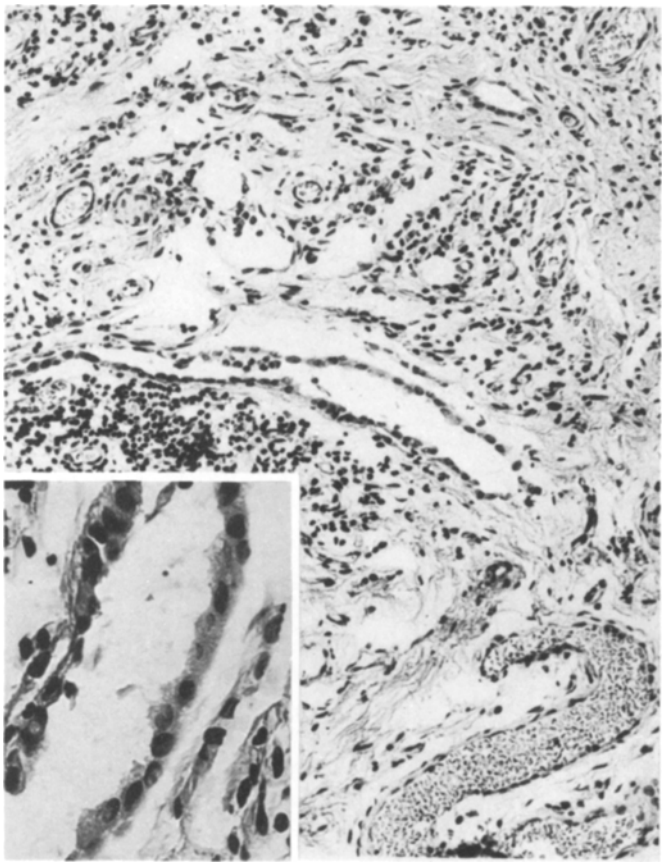


Fig. 9. Case 5: Pleura with inflammatory changes showing small spaces lined by activated mesothelial cells. Inset: Note the large and dark nuclei of the mesothelial cells. H & E ×100 (inset ×320)

diffuse malignant mesothelioma. In Cases 1, 2 and 3, the tumor was of the epithelial type (Figs. 1, 4, 7) and in Cases 4 and 5, it was of a sarcomatous type (Figs. 8, 11). The mucin stain was negative in all specimens from the five cases. The other special stains appeared to have little significance in the diagnosis of malignant mesothelioma.

Electronmicroscopic examinations of the neoplastic tissues from Cases 2, 3, 5 were done on the surgical material; in Case 4, on the autopsy material. The first two tumors showed cells with features of irritated mesothelial cells (Fig. 12). It was more difficult to ascertain the cell of origin in Cases 4 and 5; however, a few cells were present with long villi and prominent desmosomes which are the hallmarks of mesothelial cells.

Discussion

It was of interest to compare the tissue diagnosed as benign with the tumorous structures since such a correlation may provide useful criteria for the early

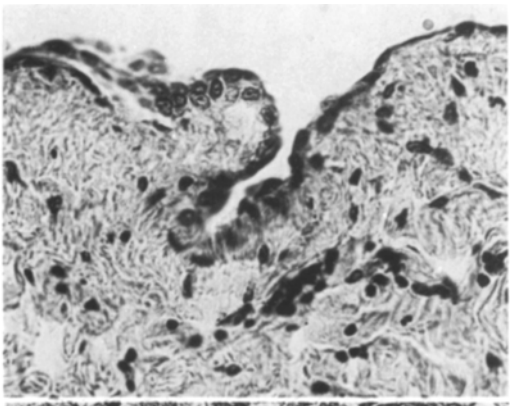


Fig. 10. Case 5: Focal mesothelial prominence on the surface of the resected pleura. H & E ×250

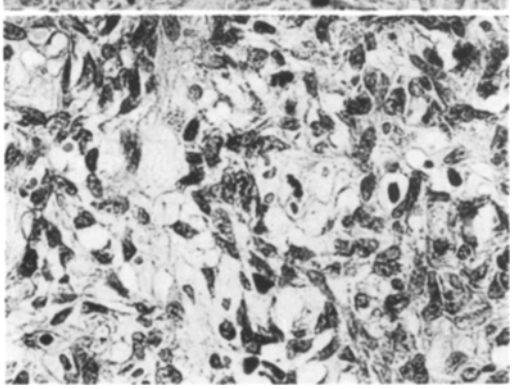


Fig. 11. Case 5: Sarcomatous type of mesothelioma. The tumor is composed of fibrocytic looking cells characteristically arranged in a loose pattern. H & E ×500

diagnosis of mesothelioma. To our knowledge, only Hourihane (Hourihane, 1965) compared benign and malignant morphological features of pleural lesions. Ratzer (Ratzer et al., 1967) observed transitions from normal mesothelium through hyperplastic mesothelium into a mesothelioma. Do our cases represent early unrecognized stages of malignant mesothelioma? We examined many samples of the specimens and we were not able to identify the presence of tumor. Neither of the "benign" lesions reviewed could have been diagnosed as neoplastic. Ratzer et al. (1967) mention a similar patient who developed a mesothelioma four years after a previous thoracotomy for pneumothorax in which he was unable to find evidence of malignancy in the tissue from the first surgery.

The lesions were categorized as pleural adhesions (Case 1), focal mesothelial hyperplasia (Case 5) and most commonly as chronic pleuritis. However, with the advantage of a retrospective study and with our special interest in pleural lesions, we were able to depict certain features which should arouse the attention of the pathologist in diagnosing pleural lesions. These features are areas of prominent mesothelial cells on the surface and/or lining small cystic spaces in the inflammatory exudate and among fibrous adhesions which were, until now, routinely considered as normal mesothelial reaction. Accordingly, the entrapped mesothelial cells in the organizing exudate in Case 2 (Fig. 6) do not differ significantly from the neoplastic cells in this patient (Fig. 4); however,

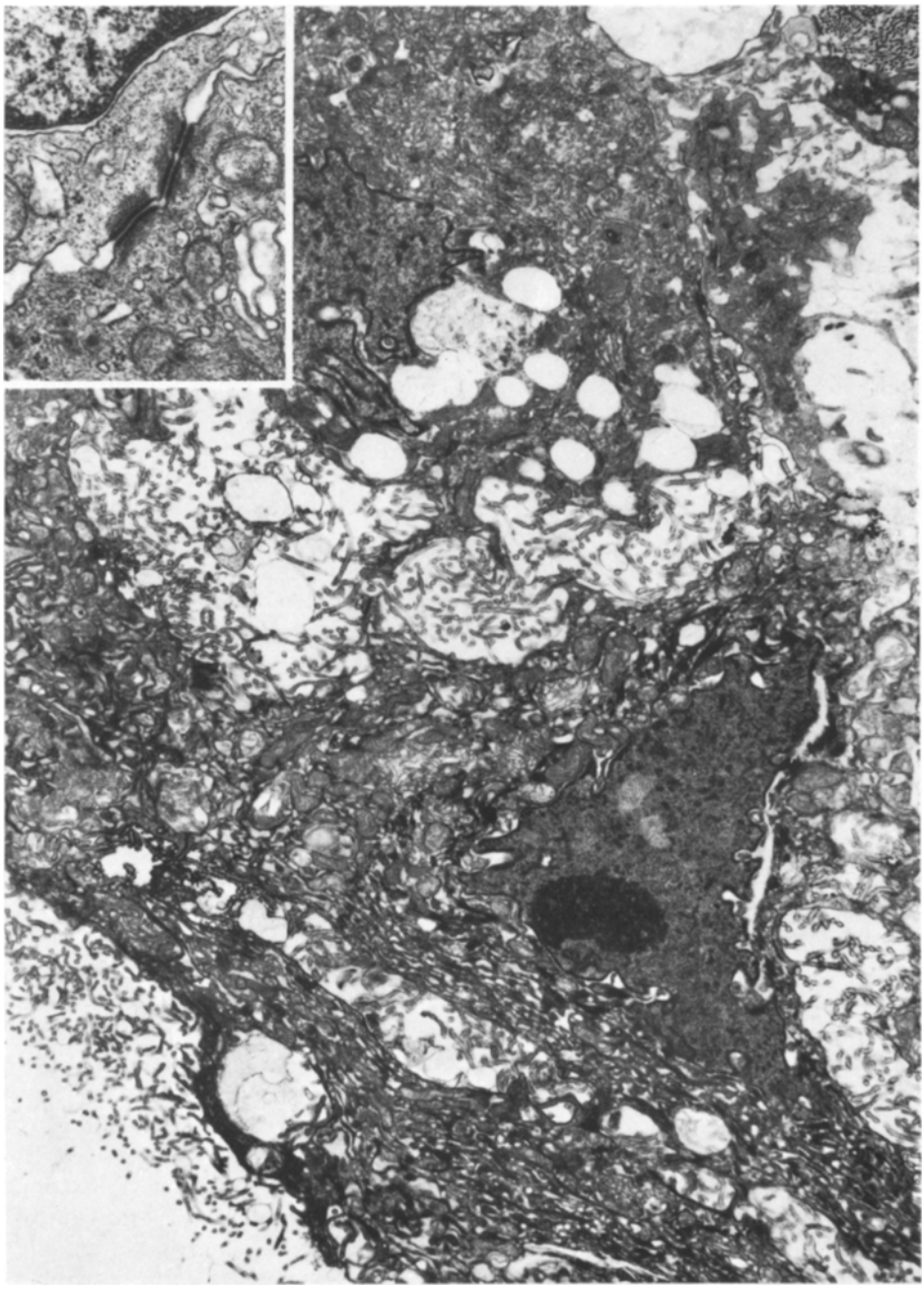


Fig. 12. Case 3: The typical electronmicroscopic features of mesothelial cells.: large amount of slender and long microvilli and desmosomal attachments (inset) ×24,000 (inset ×28,800)

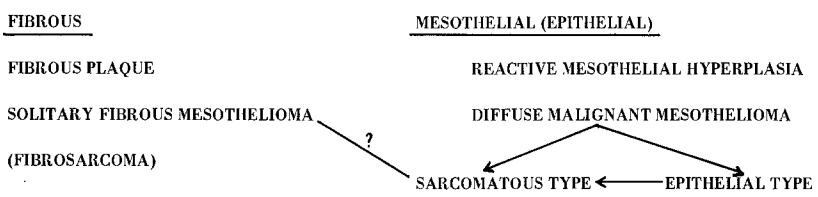


Fig. 13. Two types of pleural reactions

the overall histological features in the original lesion did not justify the diagnosis of neoplasia. We consider the piling and aggregation of the mesothelial cells, the differences in their size, the nuclear hyperchromasia, and the presence of mitoses important warning signs in the evaluation of the biopsy. Similar features were ascribed by Naylor (1968) to the malignant mesothelial cells in pleural fluids.

As we attempted to classify the different pleural lesions in relation to the development of mesothelioma, we observed that the serosa indeed reacted in two ways (Efrati et al., 1976; Stout et al., 1942) (Fig. 13). The most frequently seen lesion is probably the fibrous plaque which is asymptomatic and represents an accumulation of collagen, a scar-like lesion (Robinson, 1972). Mesothelial cells were not recognized in this lesion by light and electronmicroscopy. The tumorous representative of this fibroreactive group of lesions would be the solitary benign fibrous mesothelioma. It is a distinct and well recognized tumor (Stout et al., 1942) attached to the serosal surface by a stalk. It usually forms a large intrapleural mass and contains large amounts of collagen. The cells are arranged and squeezed along the thick collagen bundles (Figs. 14, 15). On electronmicroscopy, they represent mesenchymal fibroblastic cells (Hernandez et al., 1974). The malignant counterpart, a fibrosarcoma which we saw once only, does not have a specific morphologic feature to separate it from fibrosarcoma arising in other sites. It is rare in the pleura.

The other group of lesions develops from the mesothelial (epithelial-like) cells. Reactive mesothelial cell hyperplasia is very common and even a slight irritation to the serosal surface initiates cellular activation (Rosai et al., 1975). Although several authors mention the benign mesothelioma (Ashby, 1973; Becker et al., 1976; Foster et al., 1960; Ratzer et al., 1967), no distinct epithelial type of this benign mesothelioma has been described.

On the other hand, the diffuse malignant mesothelioma is well-defined. It is a diffusely spreading tumor originating more often in the parietal than in the visceral pleura. It covers the serosal surfaces rapidly and when infiltrating, it invades more readily the soft tissues of the thorax than the viscera (Barret, 1970; Klima et al., 1976). Histologically, it appears in an epithelial (eventually glandular) form resembling a carcinoma, or, in a sarcomatous form resembling a cellular and undifferentiated sarcoma (Klima et al., 1976; Stout et al., 1942). The electronmicroscopy in the first type is specific and shows prominent features of mesothelial cells; namely, numerous long and eventually branching villi and desmosomes (Legrand et al., 1974; Wang, 1973). In the sarcomatous type, the ultrastructure varies. Mostly, the cells do not show any specific differentiation

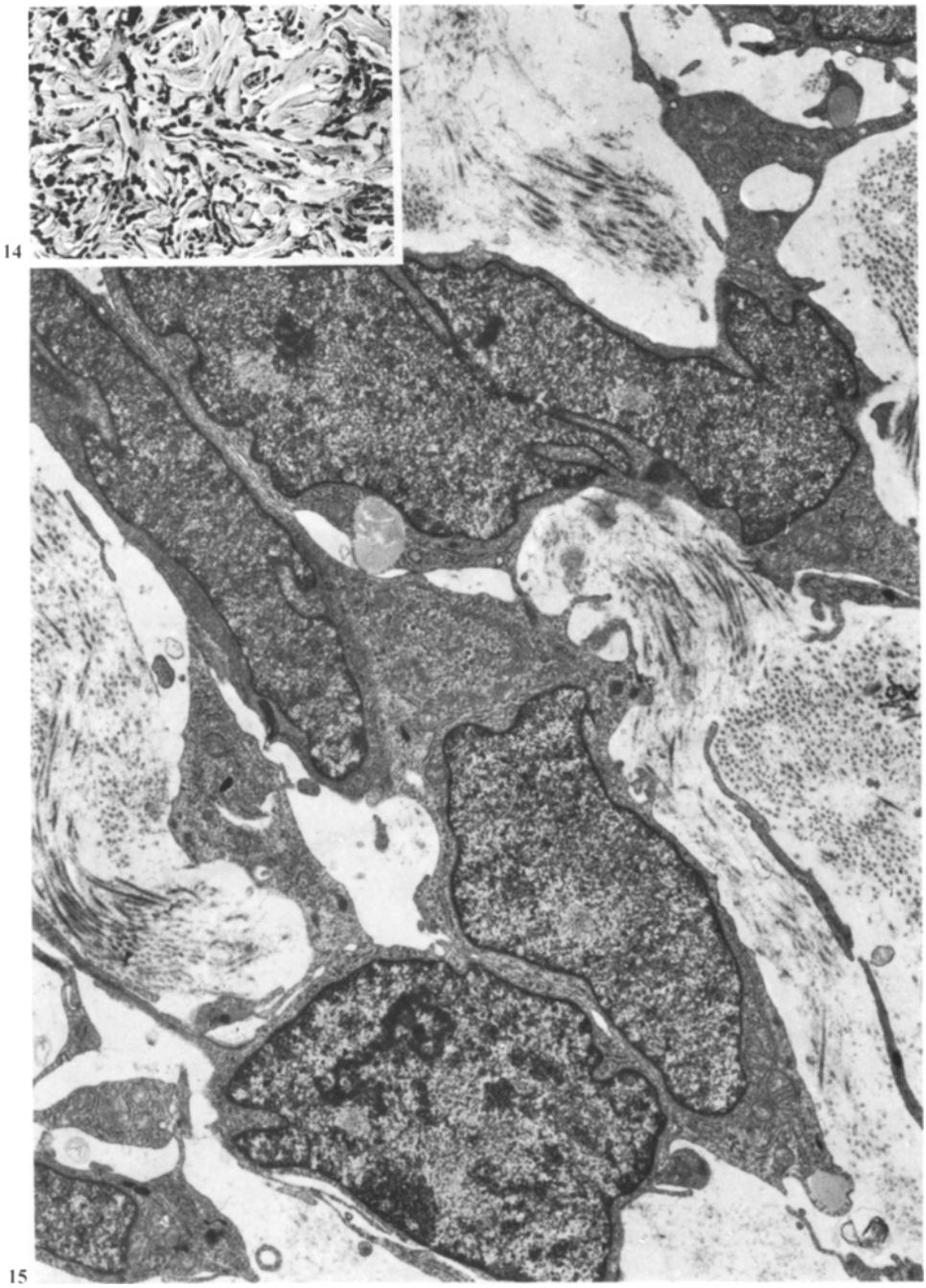


Fig. 14. (Inset) Typical benign fibrous mesothelioma with thick bundles of collagen. H & E ×52

Fig. 15. Electronmicrograph showing the mesenchymal type of cells. Note the narrow cytoplasmic extensions and the scant organelles in the cytoplasm. ×16,800

(Klima et al., 1976). If more tissue blocks are examined carefully, some mesothelial cells or incomplete mesothelial cell characteristics can be found (Kay et al., 1971). There is a lack of unanimity in the histogenetic classification of these latter tumors (Foster et al., 1960; Godwin, 1957; Kay et al., 1971; Shearin et al., 1976; Stoebner et al., 1970; Wanebo et al., 1976). We believe that the sarcomatous type illustrates best the biphasic potential of the mesothelial cell. It is questionable and even doubtful in view of electronmicroscopy (Kay et al., 1971; Klima et al., 1976) whether this type of tumor represents the malignant counterpart of a benign solitary fibrous mesothelioma.

Based on these studies, it appears that the serosal lesions reflected by a mesenchymal and fibroplastic proliferation tend to remain benign while the epithelial proliferation has a definite malignant potential. Therefore, the patients who have prominent mesothelial cell lesions in their biopsies, especially those with crowding of the mesothelial cells, should be followed closely with repeat examinations to rule out the possible development of a malignant mesothelioma.

The available experience with malignant mesotheliomas does not establish clearly what preventive treatment should be attempted in these patients. Our small series of five patients does not allow any conclusions since the therapeutic results are controversial. One of our patients survived 11 years from the first surgery. We examined specimens from another patient who had a malignant mesothelioma diagnosed 8 years ago and who is surviving after seven thoracotomies. Similar cases are described in the literature occasionally (Butchart et al., 1976; Elmes et al., 1976; Ratzer et al., 1967). However, two of our five patients developed the tumor rapidly despite extensive treatment of the pleura during the first surgery. More clinicopathological correlation is needed to establish the factor which influences the longer survival in one case and the rapid spread of the tumor in another case. Radiation therapy and chemotherapy have not proved to be effective in malignant mesothelioma (Butchart et al., 1976; Elmes et al., 1976; Ratzer et al., 1967; Shearin et al., 1976); although there are reports to the contrary (Briney, 1974; Fontana et al., 1976; Kucuksu et al., 1976).

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