

LOCALIZED PRIMARY TUMORS OF THE PLEURA

An Analysis of 40 Cases

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A study of 40 localized primary tumors of the pleura in the files of the Canadian Tumour Reference Centre revealed a considerable diversity in their histologic structure. Collagenized, hemangiopericytoma-like and cellular areas were the main forms of growth pattern, with half of the tumors showing a mixture of two or more of these elements. Inclusions of non-neoplastic bronchiolo-alveolar epithelium were frequently seen in areas of tumor adjacent to lung substance but in only one tumor was there a neoplastic component of epithelial form. Eight tumors (20%) showed evidence of malignant behavior. All of these were large and cellular at the time of initial surgery and four had mitotic counts of 10 or more/10 H.P.F. in areas. The evidence suggests that the great majority of localized pleural tumors arise from submesothelial mesenchymal elements and it is believed that the term mesothelioma should not be used in reference to these growths.

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P RIMARY PLEURAL TUMORS occur in diffuse and localized forms. The first, the diffuse mesothelioma, is a malignant growth which encases the lung and may assume the histological characteristics of a carcinoma, a sarcoma, or both. Similar growths occur not infrequently in peritoneum and occasionally in pericardium and tunica vaginalis. Diffuse mesotheliomas have attracted much interest because of their prevalence in subjects exposed to asbestos.

Localized pleural tumors, in contrast, present as circumscribed masses and often appear to follow a benign course. They are rare, the incidence being only 2.8 cases per 100,000 registrations at the Mayo Clinic.¹⁵ The majority

arise from visceral pleura and many project into pleural cavity as pedunculated masses. A small number of tumors may be mainly or entirely intrapulmonary.^{2,5,15,19} There are relatively few detailed accounts of the histology of localized tumors. Most appear to be predominantly fibrous but with varying cellularity.^{5,15} A small number of epithelial or biphasic forms have also been described.^{1,5,15,24} Evidence of a significant association with asbestos exposure has not been recorded. Localized tumors have been reported only rarely in other serosal cavities.¹⁸

Though the overall gross and microscopic characteristics of localized neoplasms are strikingly different from those of diffuse mesothelioma, evidence derived from tissue culture,²⁰ and light^{5,15} and electron microscopy^{9,11,16} has encouraged the view that the localized growth is also of mesothelial origin and the designation "localized fibrous mesothelioma" is widely used. However, some observers continue to support the view of Klemperer and Rabin¹⁰ that localized fibrous tumors arise from submesothelial connective tissue and terms such as "localized fibrous tumor of pleura"⁷ or "benign local pleural fibroma"¹⁷ are sometimes applied to the growths. Localized soft tissue tumors of various types, including lipoma,¹⁰ hemangiopericytoma,¹² and rhabdomyosarcoma,³ have occasionally been reported in relation to the pleura.

This paper describes a group of 40 localized

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TABLE 1. Main Characteristics of 40 Localized Primary Tumors of Pleura

CTR no.	Sex	Age	Size/weight of tumor	Histology			Evidence of malignancy
				C	F	H	
266	M	66	21 × 13 cm; 1160 g	X			None 5 yr p-o.
1096	M	37	4500 g		X		None. Autopsy dx.
3127	M	5	10 cm; 500 g	Like synovial sarc.			Yes at 2¼ yr p-o.
4001	M	58	190 g	X			None 12 yr p-o.
4488	M	67	58 g		X		None 4½ yr p-o.
4805	M	24	2.0 × 2.4 cm		X	X	None 10½ yr p-o.
6925	M	31	600 g	X			Yes at 1 yr p-o.
10101	F	67	870 g	X	X		None 7 yr p-o.
10132	F	57	2.5 × 1.7 cm	X	X	X	None 4 yr p-o.
10134	M	43	2.5 cm		X		None 5½ yr p-o.
10196	F	57	3.5 × 2.0 cm		X		No follow-up
10692	M	66	3810 g	X	X	X	Yes at 10 yr p-o.
10924	M	87	410 g	X			None. Autopsy dx.
10968	M	65	12.0 × 11.0 × 6.5 cm		X		No follow-up
10969	M	42	8 × 7 × 4 cm	X	X		None 17 yr p-o.
11606	F	45	Not known	X	X		None 8 yr p-o.
11932	F	52	5.5 × 5.0 × 2.4 cm		X	X	None 11 yr p-o.
12388	M	60	10 × 7 × 5 cm		X	X	None 10 mo p-o.
13133	M	58	14.0 × 9.0 × 6.5 cm	X	X	X	None 8½ yr p-o.
14043	F	24	Very large	X			Yes at 13 yr p-o.
14052	M	87	21 × 18 × 9 cm	X	X		None. Autopsy dx.
14055	M	80	8 × 5 × 4 cm	X			None. Autopsy dx.
14212	F	31	4 cm	X			No follow-up
15339	M	68	25 × 16 cm; 2600 g	X			None. Autopsy dx.
15574	F	51	7.8 × 5.7 × 4.3 cm		X		None 2 yr p-o.
16323	M	69	2.5 cm		X		No follow-up
16415	F	50	7 × 6 × 4 cm		X		None 3½ yr p-o.
16812	M	57	18.0 × 12.0 × 11.5 cm	X		X	Yes at 4½ yr p-o.
16992	M	42	5 × 2 cm		X		None 2 yr p-o.
17103	F	60	8 × 7 × 5 cm	X	X	X	None 1 yr p-o.
17373	M	49	6 cm; 60 g			X	None 7 yr p-o.
19341	M	66	14 cm; 670 g	X	X		Not known. Dead
20315	M	62	Large tumor	X		X	Yes at 1 yr p-o.
20794	F	74	26 × 16 cm; 2650 g	X	X		Yes at 19 mo p-o.
21658	M	58	5 cm	X	X		None 1½ yr p-o.
21994	F	34	9 × 6 cm	X		X	No follow-up
22607	F	40	3 cm	X			No follow-up
22632	M	56	14 × 10 × 7 cm	X	X		No follow-up
23173	M	74	13 × 12 × 11 cm	X	X		Yes at 6 mo p-o.
23641	M	30	3.0 × 2.0 × 1.2 cm	X	X	X	No follow-up

C: cellular; F: fibrous; H: hemangiopericytomatous; p-o: postoperatively.

primary pleural tumors. The diversity of their histologic structure is a feature of particular interest.

MATERIALS AND METHODS

The material was collected during a review of the 370 pleural tumors in the files of the Canadian Tumour Reference Centre. Forty of the growths met the criteria for inclusion in the study in that they were primary non-carcinomatous neoplasms which formed a single localized mass in contact with pleura. Several other cases of apparently localized pleural tumors were excluded from

the present study because they were multinodular or formed poorly defined masses whose ramifications were not clear. A few cases were also excluded because of inadequate documentation.

In 35 cases, the primary growth had been removed surgically; in the remaining five it was first characterized at autopsy. In most cases the file material appeared to represent an adequate sampling of the tumor, with between three and eight hematoxylin and eosin sections from different areas being available. In many cases, reticulin, trichrome and periodic acid Schiff preparations were also examined.

Follow-up information for postoperative periods ranging between 6 months and 17 years (mean 5.5 years) was obtained in 27 of the 34 surgically resected cases.

RESULTS

Clinical Findings

The 40 subjects ranged in age from 5 to 87 years (mean 53.7) at the time their tumors were first recognized. There was only one case below the age of 20. There were 27 males and 13 females. The tumors were right-sided in 24 cases and left-sided in 15. Some additional clinical information was available in many cases. Around one-fourth of patients had apparently been asymptomatic, their tumors having been discovered incidentally on chest x-ray. In patients who were symptomatic, dyspnea and ipsilateral chest pain appeared to be the most frequent complaints. Ipsilateral pleural effusion, occasionally blood stained, accompanied a number of the larger tumors and compression of the inferior vena cava with ascites and leg edema was noted in two cases. Three patients presented with manifestations of hypoglycemia. The presence of finger clubbing was occasionally documented.

Gross Findings

Tumor weights or measurements were available in most instances and are summarized in Table 1. Weights ranged between 4 and 4,500 g and maximum diameters between 2.5 and 25.0 cm. The growths appeared to be at-



FIG. 1. CTRC 1096. Bosselated pleural surface of tumor with prominent blood vessels.

tached to parietal pleura in five cases and to visceral pleura in 28. In the remaining seven cases, the point of attachment was not stated or the tumor was noted to have been adherent to both layers of pleura. The tumors generally appeared to be round with a smooth pleural surface. Bosselation and prominent superficial blood vessels were sometimes noted (Fig. 1). Eighteen of the 40 tumors (45%) lay mainly or entirely in the pleural cavity where they often formed pedunculated masses. All but two of the latter group were attached to the visceral pleura. Eight growths (20%) projected to some extent into both pleural cavity and lung substance. Three tumors (7.5%) were entirely intrapulmonary but came in contact with pleura at some point. In the remaining

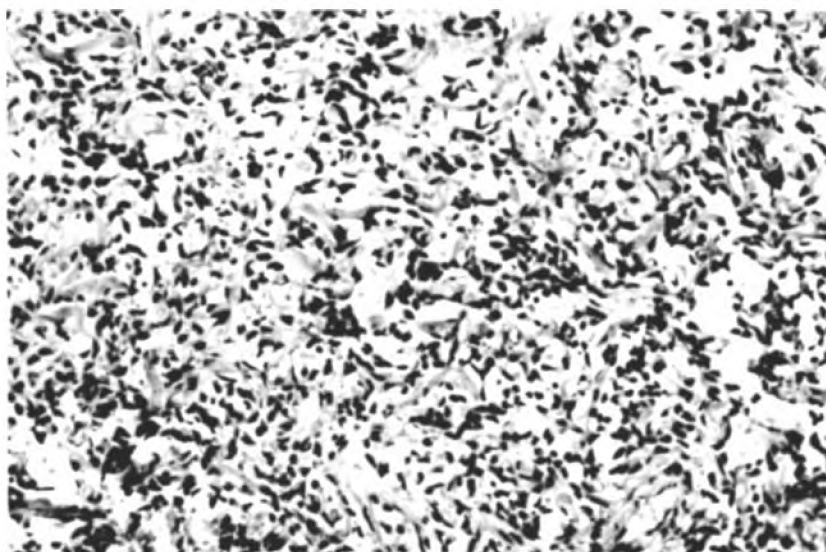


FIG. 2. CTRC 11932. Randomly disposed fibrocellular elements (H & E, $\times 180$).

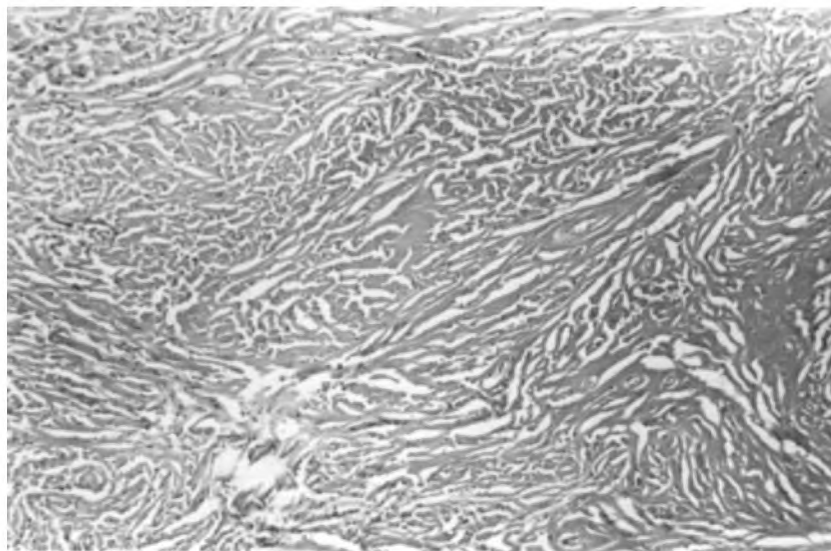


FIG. 3. CTRC 10924. Distinctive complex pattern formed by collagen bundles (H & E, $\times 75$).

11 cases (27.5%) the extent to which tumor projected into pleural cavity was not clear. Most tumors were solid and their cut surfaces were sometimes said to show a whorled pattern. Tiny areas of hemorrhage or softening were occasionally seen. Cystic change was noted in two cases and in one of these was associated with a most unusual appearance. This growth was bilobed with one solid end and the other riddled with small cystic spaces. It projected into pleural cavity from parietal pleura and had a short band-shaped pedicle. Tiny satellite nodules were noted in the immediately adjacent pulmonary parenchyma in two cases.

Microscopic Findings

There was a marked variation in the appearance of the tumors. Collagenized, hemangiopericytoma-like and cellular areas were the main forms of growth pattern observed. Many tumors showed a mixture of two or more of these patterns (see Table 1).

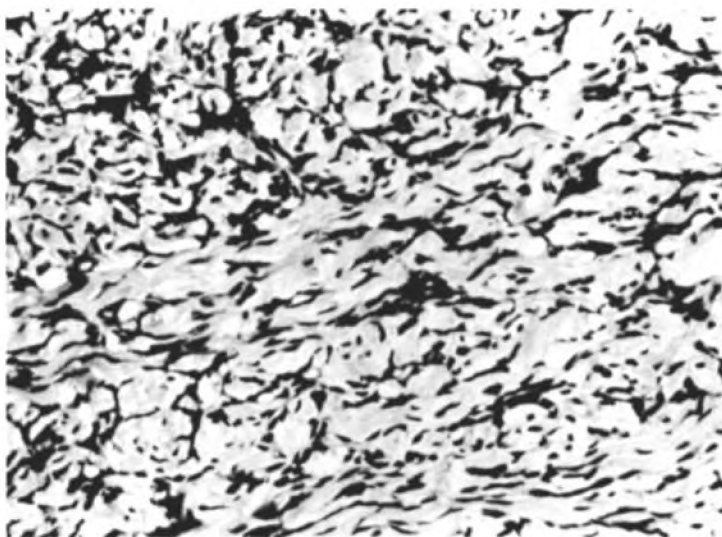
Fibrous or collagenized areas were seen in most cases and in nine (22.5%) they were predominant. The appearance of the fibrous element was sometimes nondescript, haphazardly and loosely arranged spindle- or oval-shaped cells being separated by strands of collagen (Fig. 2). Quite frequently, however, there was a more striking and unusual pattern in which bundles of dense hyalin collagen were disposed in whorls and other complex patterns (Fig. 3). The cellularity of the latter areas varied greatly. In the most cellular foci, the collagen bundles were separated by

prominent clusters of small or medium sized oval or fusiform cells with hyperchromatic nuclei which sometimes appear compressed between bands of collagen (Fig. 4). In a few cases fibrocellular elements took up a storiform pattern in areas (Fig. 5).

Areas similar or identical to those seen in a hemangiopericytoma (Fig. 6) were noted in 12 tumors (30%). Such areas contained numerous rounded or branching vascular spaces with variable numbers of compact round or fusiform cells in the intervening tissue. Frequently, the vessels were encircled by a collar of loose faintly staining tissue, which, when associated with a "staghorn" vascular pattern, further heightened the resemblance to hemangiopericytoma. The reticulin pattern was also typical of this type of growth (Fig. 7). Vascular parts of a tumor usually showed gradual merging into fibrous or cellular areas but in one case the tumor appeared to be entirely of hemangiopericytomatous character. In a few instances vascular areas of tumor became highly cellular and small numbers of mitoses were noted.

Twenty-six tumors (65%) contained cellular areas composed of closely packed oval or spindle cells of varying size (Fig. 8). Though sometimes arranged in anastomosing or interdigitating fascicles, the cells were often randomly disposed. Nine tumors (22.5%) were almost entirely of cellular character. Not infrequently, considerable mitotic activity (2–15/10 H.P.F.) was noted in the cellular parts of tumors. Moderate nuclear pleomorphism was also occasionally seen. Reticulin sometimes

FIG. 4. CTTC 20794. Fibrocellular area with rows of compressed nuclei between thick collagen bundles (H & E, $\times 180$).



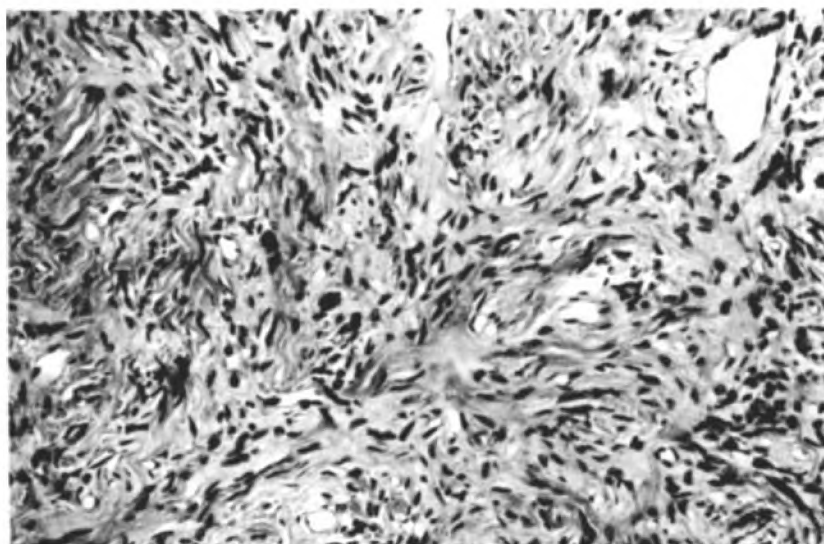
surrounded small groups of cells in cellular areas rather than forming a pericellular network (Fig. 9).

Corresponding to gross observation, foci of degeneration and cystic change were seen in a few cases. Recent necrosis was also noted in several of the more cellular tumors and occasionally in large, less cellular or more fibrous growths.

Irrespective of histological type, the pleura overlying or investing these tumors showed fibrous thickening. Surface mesothelium, however, was always inconspicuous. In those tumors related to visceral pleura, the boundary between tumor and lung substance was sharply demarcated but non-encapsulated. In many cases, at least some part of the pulmonary

aspect of the tumor was covered by a single layer of cuboidal or low columnar epithelium (Fig. 10) and not infrequently irregular cleft-like spaces lined by this epithelium were seen to dip into the substance of the growth (Fig. 11). Such ingrowths cut transversely seemed to account for the finding of isolated tubular elements in the substance of those parts of the tumor close to the junction with lung substance (Fig. 12). Occasionally, direct continuity between the epithelium lining clefts and adjacent bronchiolo-alveolar epithelium could be seen (Fig. 11). Cleft-like spaces or tubules lined by the epithelium were never found along the aspect of tumors covered by visceral pleura or in any part of those tumors arising from parietal pleura. It is clear that

FIG. 5. CTTC 19341. Storiform pattern in fibrocellular area of tumor (H & E, $\times 180$).



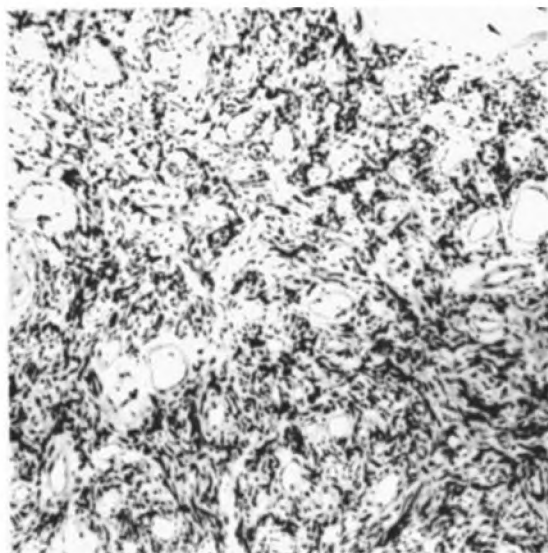


FIG. 6. CTCRC 21944. Hemangiopericytomatous area in tumor. Numerous rounded and branching vascular spaces are seen (H & E, $\times 120$).

these clefts and spaces represent inclusions of bronchiolo-alveolar epithelium and that they are not part of the neoplastic process.

One case was unique in that the epithelial component of the tumor was much more conspicuous and obviously neoplastic. In this growth, epithelial elements were distributed through a cellular sarcoma-like spindle cell matrix, the appearances mimicking closely those of a biphasic synovial sarcoma (Fig. 13). This was the case which occurred in a 5-year-old child.

Unfortunately, histological material was not available from the satellite nodules noted grossly in two cases.

Electron Microscopic Findings

Electron microscopy had been performed on fibrous or cellular areas from three tumors. In each case the cells appeared to be of fibroblastic character with no evidence of mesothelial differentiation.

Clinico-Pathological Correlation

The nine tumors of predominantly fibrous character all arose from visceral pleura. Most of these appeared to lie mainly or entirely within the pleural cavity and four were said to be pedunculated. Other pedunculated growths showed the same range of cytoarchitectural patterns as the general body of the material. The three entirely intrapulmonary tumors were all cellular. With these exceptions there was no obvious correlation between location and gross and microscopical appearances.

Eight tumors showed evidence of malignant behavior. There was intrathoracic recurrence in six cases and in three of these, as well as two other cases without local recurrence, evidence of tumor metastases was noted clinically. Local recurrence was obviously very extensive or multifocal in four cases and in one case was associated with infiltration of the chest wall. Metastases were widespread in two cases with involvement of contralateral pleura, liver, adrenal, small intestine and bones in one

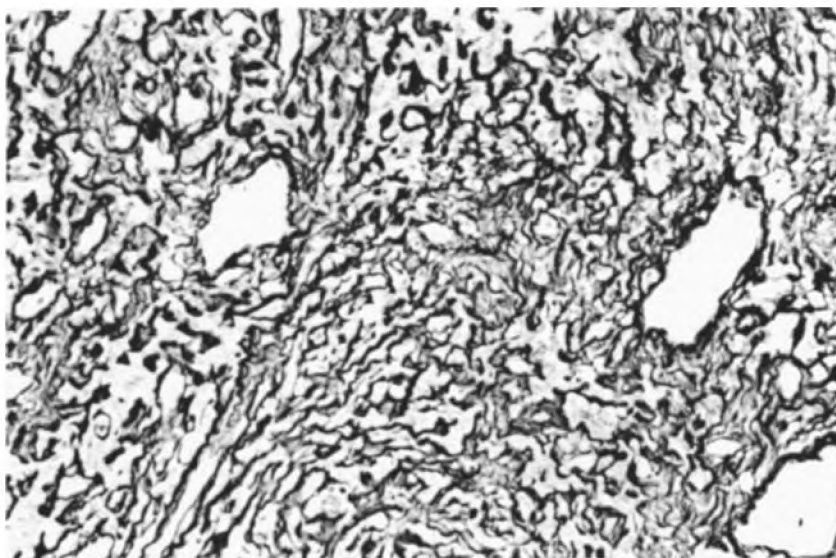
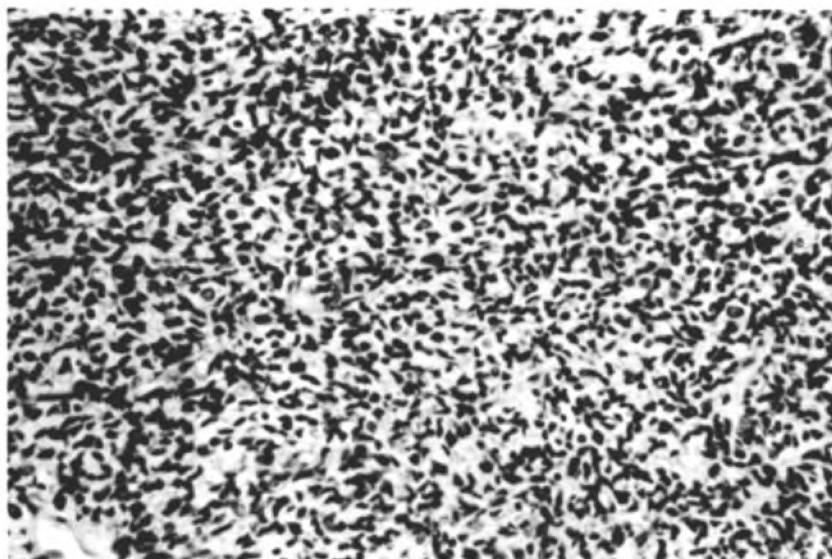


FIG. 7. CTCRC 21944. Reticulin pattern typical of hemangiopericytoma (Bielschowsky, $\times 180$).

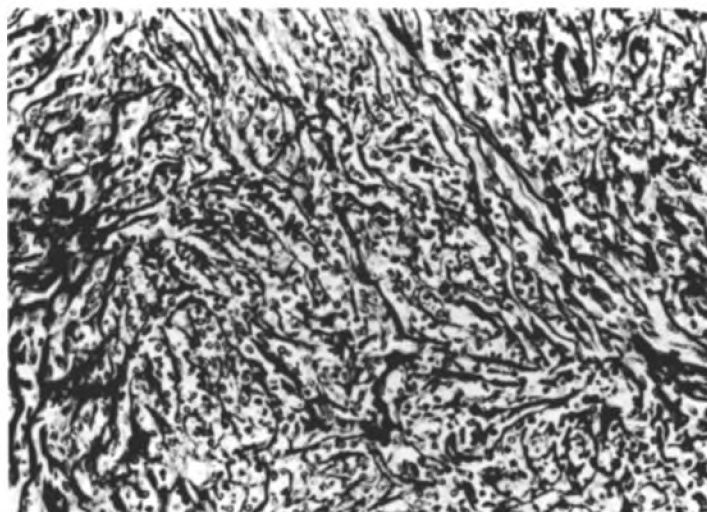
FIG. 8. CTTC 20794. Randomly disposed cells in cellular areas of tumor (H & E, $\times 180$).



and contralateral lung, liver, myocardium, skin, bone and stomach in the other. In two of the other three cases with metastases dissemination was apparently confined to the opposite pleural membrane. Local recurrence or metastases were found at periods ranging between 6 months and 13 years following surgery. All eight malignant growths were large at the time of initial surgery, the smallest being 10 cm in diameter and the largest weighing 3810 g. In seven cases the main mass of tumor lay within the pleural cavity with one growth being described as pedunculated. Included in this group is the tumor in a child whose resemblance to synovial sarcoma is noted above. It formed an encapsu-

lated mass 10 cm in diameter adjacent to the diaphragm which appeared to arise from the inferior pulmonary ligament or paravertebral gutter. The other seven malignant tumors also contained highly cellular areas. In two cases these areas retained evidence of a hemangio-pericytomatous character. In the others, they were composed of oval or fusiform cells usually of medium size and sometimes disposed in interdigitating fascicles and showing some degree of nuclear pleomorphism. In four of the seven cases, mitotic counts of 10 or more/10 H.P.F. were present in cellular parts of the tumor. In the remaining three cases, including one with metastases, the highest counts were in the range of 1–4/10 H.P.F. Similar

FIG. 9. CTTC 16812. Reticulin surrounding groups of cells in cellular area of tumor (H & E, $\times 180$).



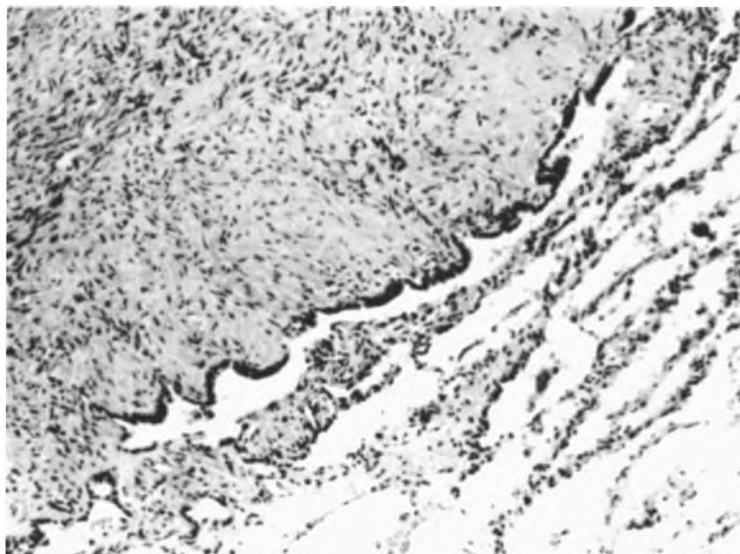


FIG. 10. CTCRC 10924. Epithelium covering surface of tumor where it abuts on lung (H & E, $\times 75$).

counts were obtained in the cellular areas of three tumors which are not known to have recurred or metastasized. Foci of recent necrosis were noted in most of the malignant growths.

All three tumors associated with hypoglycemia were very large (3810 g; 2650 g; 2600 g). Two belong to the malignant group described above and all showed highly cellular areas.

DISCUSSION

These localized pleural tumors show considerable variation in histological pattern and, in this respect, are comparable to diffuse pleural neoplasms. However, the cytoarchi-

tectural patterns of the two groups have little in common. Though diffuse mesotheliomas may have a sarcomatoid appearance the majority are of epithelial or carcinosarcomatous (biphasic) form.^{8,23} Localized tumors rarely contain neoplastic epithelial elements (as opposed to inclusions of non-neoplastic bronchiolar epithelium). Most localized growths are of fibrocellular or sarcomatous character and they often show distinctive histological characteristics. The latter include complex dispositions of collagen in fibrous areas and the blend of tissue patterns which is frequently present.

Several observers have mentioned that

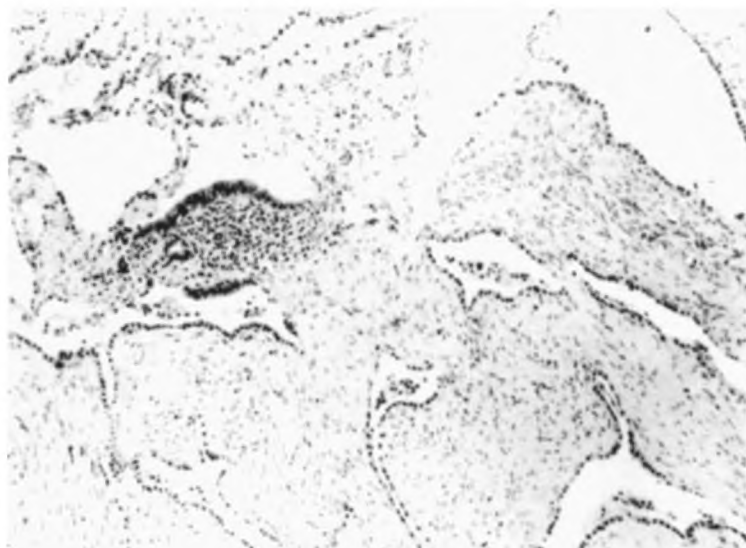
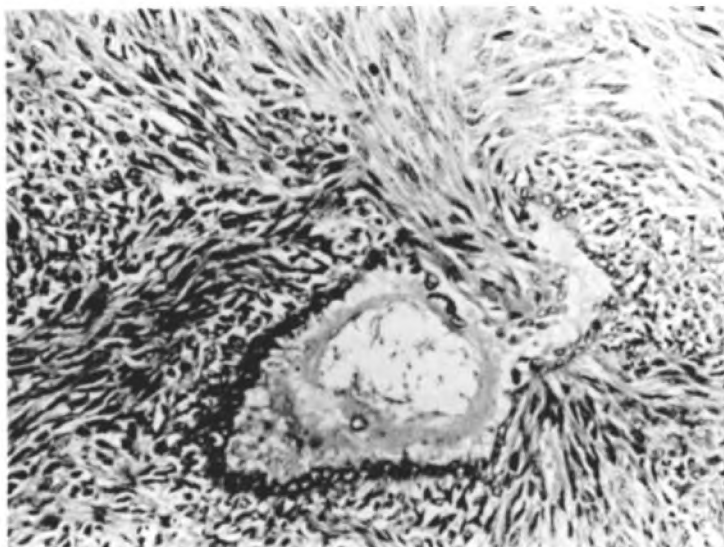


FIG. 11. CTCRC 10196. Cleft-like spaces lined by epithelium dip into the substance of the tumor. Continuity with bronchiolo-alveolar epithelium is seen at center left (H & E, $\times 75$).

FIG. 12. CTRC 19341. Isolated tubule in the substance of cellular tumor (H & E, $\times 180$).

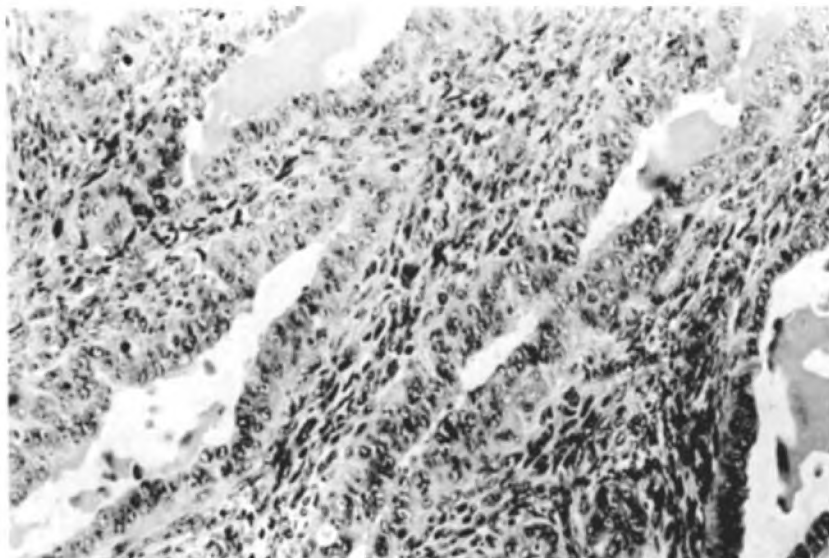


pedunculated localized mesotheliomas may imitate the appearance of hemangiopericytoma.^{4,19} There have also been occasional reports of pulmonary hemangiopericytomas which come in contact with pleura.¹² Otherwise, little attention has previously been paid to the vascular component of localized pleural tumors. In our material, 30% of the growths showed areas identical to those seen in hemangiopericytoma. Localized pleural tumors thus share the capacity to develop a hemangiopericytomatous pattern with a number of other tumors, including synovial sarcomas, mesenchymal chondrosarcomas, thymomas, and angioblastic meningiomas. However, as far as

we know, a hemangiopericytomatous structure has not been seen in diffuse mesotheliomas.

In spite of the histological diversity of this group of pleural tumors, we believe that the great majority share a common histogenesis. The best evidence of this is the frequency with which combined and overlapping cyto-architectural patterns occur and the similar gross morphology of many of the tumors. An exception could be made in respect to the three intrapulmonary tumors in our material, all of which were predominantly cellular growths lacking the hemangiopericytomatous or distinctive fibrous patterns seen in many of the other tumors. However, it should also be

FIG. 13. CTRC 3127. Tumor with a biphasic pattern resembling that of synovial sarcoma. This was the only tumor showing a neoplastic epithelial component (H & E, $\times 180$).



stated that the appearance of the intrapulmonary growths was not particularly suggestive of any other form of mesenchymal or pulmonary tumor.

Stout and Himadi¹⁹ refer to five intrapulmonary tumors of serosal origin and noted that they were all cellular anaplastic spindle cell growths whose appearance suggested malignancy. Tissue culture studies of one growth had suggested²⁰ that the cells were of mesothelial character and these workers retained the designation of mesothelioma for the intrapulmonary form of localized tumor. Foster and Ackerman⁵ included five apparently intrapulmonary tumors in their series of 18 localized mesotheliomas of pleura and pointed out that, although they did not resemble any of the known pulmonary parenchymal neoplasms, they did resemble the other localized pleural tumors which they described. Malignant characteristics were no more prominent in the deeply situated group. However, Guc-cion and Rosen⁶ noted that intrapulmonary spindle cell tumors with visceral pleural involvement have a relatively high grade of malignancy as compared with localized tumors found only in the pleural space and they suggested that this favored a pulmonary rather than a mesothelial origin. None of our three intrapulmonary tumors has as yet shown biological evidence of malignancy but the follow-up period in two cases is less than three years. In light of existing evidence, it seems wise to keep an open mind about the validity of including these intrapulmonary neoplasms with the group of localized pleural tumors.

Most previous reports would indicate that malignancy is rare in localized tumors which project mainly or entirely into the pleural cavity. However, local recurrence or metastases following surgery have been encountered in small numbers of cases. In several instances local recurrences of tumor have been said to be histologically benign.^{15,21} Our own experience with the behavior of localized tumors which are not entirely intrapulmonary is a rather less favorable one than that of many other observers but somewhat similar to that recently reported by Okike *et al.*¹⁵ Six of our 37 cases (16.2%) developed intrathoracic recurrences and five cases (13.5%), including three of those with intrathoracic recurrence, had evidence of metastases. Bearing in mind that some of our cases are recent or lack follow-up data and that recurrences or metastases may appear many years after surgery, our figures may well underestimate the po-

tential of these growths for malignancy. Moreover, as noted previously, we excluded several, apparently localized pleural growths from the present study because they were ill-defined or multinodular. We are uncertain at present of the status of this latter group but it seems quite possible that they may be malignant forms of localized pleural tumors.

Our experience indicates that size and cellularity are the best guide to the behavior of localized tumors. All of our malignant growths were large and cellular at the time of surgery. Four cases also showed many mitoses. Because of the variation in cellularity and mitotic activity observed in different parts of some of these tumors, the importance of adequate sampling in relation to assessment of malignant potential should be emphasized.

Hypoglycemia has been described in association with large spindle cell tumors in a number of areas including pleura.^{13,14} The fact that there were three examples of this association among our cases suggests that hypoglycemia may be a not uncommon phenomenon when localized pleural tumors grow to a large size.

Three of the 18 localized pleural tumors described by Foster and Ackerman⁵ had a papillary epithelial structure in all areas and in six other growths which were predominantly fibrous there were occasional epithelial structures or elements. These investigators believed that in these mixed tumors the epithelial elements were of mesothelial origin and not trapped lung tissue. They noted that tubular and papillary epithelial structures were always observed near the periphery of tumors rather than in their depth. We have found similar tubular elements in many of our growths with an intrapulmonary component and we have observed that these elements usually seem to occur close to the junction of tumor with lung tissue. We have also noted that the pulmonary aspect of the tumors is frequently covered by a low columnar or cuboidal type of epithelium which not infrequently lines clefts or spaces which dip into the substance of the tumor. These observations leave us in no doubt that the epithelial component of these tumors usually represents inclusion of non-neoplastic bronchiolar or alveolar epithelium. We feel that only one of our cases contains a component of epithelial form that is genuinely neoplastic. The unique histological appearance of the tumor in this case and the fact that it occurred in a child suggests that it may not belong to the same group as the other cases.

The non-epithelial character of the great majority of localized pleural tumors and the striking gross and microscopical differences between them and diffuse pleural mesotheliomas suggest that these tumors arise from submesothelial mesenchymal elements rather than mesothelium. This view concerning the origin of localized tumors was originally put forward by Klemperer and Rabin in 1931.¹⁰ The strongest arguments supporting a mesothelial origin are based on ultrastructural observations^{9,16} and reports of localized tumors which contain tubular or papillary elements of presumed mesothelial origin.^{5,24} In our own very limited experience of the ultrastructural examination of localized tumors we have so far not encountered evidence of mesothelial differentiation. We have noted tubular structures in a number of our tumors but believe that in all but one case these represent inclusions of non-neoplastic bronchiolo-alveolar epithelium. Our one case with a neoplastic tubular component of epithelial character closely resembled a biphasic type of synovial sarcoma and in fact may well be of this nature.

When it is borne in mind that synovial sarcomas usually arise from soft tissue outside synovial membranes it is clearly not necessary to postulate that the present case necessarily arose from mesothelium.

In the absence of more convincing histogenetic evidence it would seem wise to exclude the term mesothelioma in describing localized pleural tumors. Such a step would also have the sanction of avoiding confusion in relation to epidemiological and therapeutic considerations. Unlike diffuse mesotheliomas, localized pleural tumors are often benign and no evidence has emerged to suggest that they are etiologically related to asbestos exposure. The term "localized fibrous tumors of pleura"⁷ would seem to be an appropriate designation for these tumors at the present time.

There appear to be only three examples in the files of the Canadian Tumour Reference Centre of localized fibrous tumors arising in other serosal membranes. Two of these were related to peritoneum and one to pericardium. This confirms the impression gained from the literature that this occurrence is very rare.

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