METASTASIZING FIBROLEIOMYOMA OF THE UTERUS *

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Dissociation between clinical and histological malignancy in neoplasms reaches its acme in the "benign metastasizing tumors" in which the histological appearance is benign but which metastasize and prove to be clinically malignant. Among these tumors are certain chondromas, some angiomas, and "metastasizing adenomas" of the thyroid. To these must be added a few reported cases in which fibroleiomyomas of the uterus and myomas of other locations have metastasized. This report deals particularly with the problem of metastasizing fibroleiomyomas of the uterus.

As used in this paper, the term "metastasizing fibroleiomyoma" of the uterus refers to a tumor composed histologically, in both the primary growth and its metastases, of benign appearing, fully differentiated smooth muscle cells and dense connective tissue. This distinguishes it from primary leiomyosarcoma of the uterus and from sarcomas arising in fibromyomas or so-called sarcomatous degeneration of fibroids, in both of which the tumor cells have histological characteristics of malignancy in the primary tumor as well as in the metastases. Such unquestionable sarcomas lie beyond the scope of this study and will not be stressed. Instances are also recorded in the literature in which a uterine tumor was removed and called a fibromyoma after histological study, but in which local recurrences or metastases later showed histological evidence of anaplasia and malignancy. With such cases also we are not concerned in this report.

Metastasizing fibroleiomyomas of the uterus have been seen and described by several observers but their occurrence is so rare that some oncological authorities have never seen a case and have expressed doubts as to their existence. Thus Ewing [1] in discussing the possibility that uterine leiomyomas of benign appearance might metastasize states: "So far as I have been able to learn no

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case has been fully studied in which definite variations from the usual structure of leiomyoma were wanting, although in several instances these variations have not been very pronounced." Stout, in discussing the same problem, writes [2]: "While Jacquin has been able to collect 5 cases of tumors which morphologically were fibromyomas and yet metastasized and recurred always as unaltered myomas, such reports must be exceptionally rare and they leave one with the suspicion that there may be some change which has been overlooked even though the cases were reported by such keen observers as Langerhans, Minkowsky, Schlagenhaufer and von Franque." Meyer [3] and Albrecht [4] also believe that metastasis of mature myoma cells has not been proved up to the present. They believe that multiple sections from the primary tumors in the uterus in suspected cases would reveal a sarcoma in some portion. They fail, by this explanation, to account for the benign appearance of the structure in the metastases in these cases, and their lengthy discussions together with that of Raab [5] are beside the point.

Against these opinions stand the written words of a host of authorities who accept these tumors. Among them are Kaufmann,[6] Borst,[7] Aschoff,[8] Wolff,[9] Ribbert,[10] and others.

The question can then legitimately be asked whether or not such a tumor exists in the uterus or elsewhere. Since appeal to authority cannot settle this question, a critical evaluation of the cases reported in the literature, together with the new evidence obtained by study of a case, may, we hope, help clarify the subject. My attention was drawn to this problem after studying a case which seemed to fulfill the criteria for this type of neoplasm. The microscopic sections have been seen by about twenty pathologists who, suspecting that a benign myoma would not be submitted for pathological opinion, were nevertheless unable to make a diagnosis of malignancy.

Because of their rarity metastasizing fibroleiomyomas of the uterus are not of great practical importance. To the oncologist, however, they are of great interest because they illustrate certain limitations in the purely histological diagnosis of malignant disease, emphasize the inadequacy of the classical criteria for malignancy, as opposed to benignancy, remind him to be particularly cautious in the diagnosis of certain types of tumors, and

illustrate differences from accepted biological behavior in a number of interesting respects.

This paper deals with the case of a patient who exhibited the clinical picture of chronic pulmonary obstruction with cor pulmonale and polycythemia, and who died with right sided heart failure. The changes in the lungs during life suggested most strongly a chronic pulmonary infection. A symptomless pelvic mass was recognized during life but its relation to the changes in the chest was uncertain prior to autopsy. From a uterus the site of multiple tumors resembling fibroleiomyomas, massive metastases occurred to the lungs and to a tracheobronchial lymph node. The microscopic appearance of the metastases and of the uterine tumors was that commonly seen in uterine fibroids, the cells being benign in appearance and fully differentiated.

Report of Case

Clinical History: M. B., a housewife, aged 36 years and of English descent, was under observation at the University of Chicago Clinics (Unit #100,419) from March 12, 1934, until her death 15 days later. She gave a history of dyspnea, wheezing respirations, nocturnal headaches and nosebleeds during the preceding 18 months, a productive cough for about a year, marked orthopnea for 9 months and swelling of the ankles and abdomen for 6 months.

The patient had a prolonged chill accompanied by transient pain in the chest in May, 1933. During that summer she had a period of afternoon rise in temperature. She lost 77 pounds in weight between February and October, but had regained 25 pounds before her present hospital admission 5 months later. Her sputum was abundant, thick and yellowish, but not bloody. After study of X-ray films a physician had made a diagnosis of tuberculosis more than a year before her death, but no tubercle bacilli and no fungi could be found in the sputum. This diagnosis was abandoned by him in October, 1933, when X-ray films showed a slight recession instead of the expected advancement in the lung lesions. X-ray therapy to the chest was then followed by temporary subjective improvement. In January, 1934, the heart was found to be enlarged and she was decompensated, having dependent edema and an enlarged liver.

The patient stated that she had had mumps, chickenpox, measles and meningitis in childhood. She had never been pregnant. Prior to January, 1933, her menstrual periods had been regular at 30 day intervals and of 5 days duration. In January, 1933, she had a menstrual period accompanied by nosebleeds. The next periods were in May, June and July, 1933. There had been none since. Her husband was in good health. Her mother had died of diabetes at the age of 57 years.

On physical examination the patient appeared acutely ill with cardiac decompensation and advanced pulmonary disease. She was cyanotic, very dyspneic and preferred the sitting position. Examination of the eyegrounds showed tortuous vessels and an aneurysm of the left superior papillary artery.

The fingers were clubbed. Expansion of the chest, especially on the left, was diminished. Inspiration was short and expiration was prolonged. There was dullness to percussion with increased tactile fremitus over the base of the lungs. Coarse and fine moist râles, not removed by coughing, were heard in these regions. The border of the left side of the heart was 2 cm. beyond the midclavicular line. No murmurs were heard. The rhythm was normal but the rate was 110. The blood pressure was 130/80. An electrocardiogram showed a right axis deviation with inversion of T in leads II and III. The abdomen was greatly distended and there was some question as to whether it contained free or encysted fluid. The liver extended 5 cm. below the costal margin. The lower extremities showed only a slight edema. A hard tumor mass was palpable above the pubis to the left of the midline. On vaginal examination the cervix was found to be pulled up and a hard mass replaced the uterus.

The erythrocyte count was 5,680,000 and the hemoglobin was 101 per cent. The red cells showed a slight microcytosis and polychromatophilia. The leukocyte count varied between 6100 and 9200 with a differential count of 74 per cent neutrophils, 18 per cent lymphocytes, 6 per cent monocytes and 2 per cent basophils. The urine, except for a few white cells, was negative. No acid-fast bacilli or fungi were found in the thick sputum on repeated examination. The blood Wassermann and Kahn tests were negative. On attempted abdominal paracentesis a resistant mass was encountered and only a little bloody fluid which contained no unusual cells was obtained.

X-ray films made after admission showed many areas of increased density scattered throughout both lungs (Fig. 1). They were more marked in the lower lobes. There was a suggestion of bilateral cavitation. It was impossible to differentiate between tuberculosis and neoplasm from the films, although the picture was unlike that of the usual metastases to lungs. X-rays made by another laboratory in February, 1933 revealed an involvement of the lungs which already at that time resembled and was almost as spectacular as the condition shown on the last films.

The patient became more cyanotic and dyspneic, symptoms which were alleviated only by the use of the oxygen tent. The temperature varied between 100 and 102° F. and death occurred 15 days after admission to the hospital.

Postmortem Examination

The body was obese, weighing 187 pounds and measuring 162.5 cm. in length. The abdomen was protuberant with bulging in the flanks and a palpable mass was present in the midline extending upward to slightly above the level of the umbilicus. The legs and posterior parts of the body were edematous. The head and neck, the lower extremities and the back showed a marked cyanosis.

The pleural cavities had a few fibrous adhesions. The lungs were heavy and voluminous. They were everywhere studded with firm, pink to reddish tumor nodules varying in size from just visible to larger masses measuring up to 5 cm. in diameter. Intermingled with these solid masses were thin walled, semitranslucent

emphysematous sacs which showed the same variation in size. They collapsed on slight pressure. On forcing air into the lungs through the trachea these air cysts were reinflated, demonstrating their communication with the bronchial tree. They again collapsed when the pressure was released. Tumor nodules of both types, solid and cystic, projected above the surface of both lungs. A few tumors of each type were pedunculated, particularly along the lower lung margins (see Figs. 2, 3 and 4).

On the cut surfaces the solid tumors were found to be scattered throughout all lobes, but large air cysts were found only near the surface of the lung. The solid tumors were sharply demarcated but had no visible capsules. They were a reddish gray in color and the cut surface showed irregular whorls resembling a fibromyoma. Between these solid tumor nodules the parenchyma of the lung presented a honey-comb appearance because of small, thin walled air sacs. Most of the surface made by cutting was occupied by either solid tumor or cystic spaces so that there were only small, irregularly interspersed areas which appeared to be composed of functioning lung parenchyma. Frothy bloody fluid escaped from the surfaces. Each lung presented the same appearance. The right lung in addition contained a large firm mass measuring 13 by 12 by 12 cm. in the lower and lateral part of the upper lobe. This tumor contained a large cavity that was filled with a thick mucinous fluid which was sterile on bacterial culture. The walls of this cavity, while generally up to 2 cm. in thickness, showed portions as thin as 3 mm. Adjacent to this large tumor were several smaller tumors with mucinous material in their centers.

The tracheobronchial lymph nodes were slightly enlarged and several nodes showed areas of tumor tissue under the capsule resembling that seen in the lung.

The emptied heart weighed 475 gm. The increase in weight was due mainly to hypertrophy of the right ventricle, which, although the chamber was dilated, measured from 8 to 9 mm. in thickness. The left ventricle was normal in size and its wall measured 14 mm. The heart valves appeared normal. The myocardium showed no scarring and microscopically only a few small foci of mononuclear cell infiltration and a few small focal areas of fatty change were seen. The coronary arteries and aorta showed a

minimal amount of atheromatosis. The pulmonary artery and its main branches appeared normal. Their walls were thin and elastic.

The abdominal cavity contained about 600 cc. of a slightly turbid, yellowish brown fluid. The omentum was free. The intestines were cyanotic and were displaced upward by a mass arising in the pelvis from the uterus.

The liver weighed 1810 gm. Microscopically a marked hyperemia in the centers of the lobules with some necrosis in these areas, slight fibrosis, and marked fatty changes were present. The gall bladder and extrahepatic bile ducts appeared normal.

The spleen weighed 340 gm. It was cyanotic and firm and microscopically showed a diffuse fibrosis. Accessory spleens 1 and 2 cm. in diameter showed chronic passive congestion similar to that observed in the main spleen.

The gastric mucosa showed a diffuse hyperemia and numerous petechial hemorrhages. The duodenal mucosa was intensely hemorrhagic and exhibited a number of irregular erosions measuring up to 2 cm. in diameter. Throughout the remainder of the gastro-intestinal tract the walls showed variable amounts of edema, hyperemia and petechial mucosal hemorrhages.

The kidneys were cyanotic and showed also cloudy swelling with a moderate amount of granular degeneration of the epithelium of the convoluted tubules. The lower urinary tract appeared normal.

The uterus was enlarged, measuring 18 by 16 by 10 cm. (Fig. 5). Its upper surface was covered by smooth peritoneum. The uterine mass was nodular but fairly symmetrical except for nodules that projected into the right broad ligament. The surfaces made by cutting showed that it was composed of many firm nodules from a few mm. to 5 cm. in size, embedded in a fleshy fibrous stroma. The tumor nodules shelled out easily. Many of them were globular while others were elongated and irregular in contour. Closer examination showed that the tumor nodules occupied the anterior, lateral and upper walls of the uterus, and that the posterior myometrium was normally thin and muscular, measuring just over 1 cm. in thickness. The tumor nodules resembled fibroids, being firm, reddish gray, and composed of interlacing whorls of tissue. One tumor nodule showed an area of liquefaction necrosis in its center, and several others, including those

which projected into the broad ligament, were edematous. The veins in the right broad ligament were dilated and contained red ante mortem thrombi.

The uterine cavity was elongated and distorted. The endometrium was intact and normally thin, and except for a slight hyperemia was not unusual. The fallopian tubes were bilaterally thin, slender and of uniform caliber; their fimbriated ends were open and free. The ovaries were of normal appearance and on microscopic examination appeared to be functioning, having numerous ova and several small follicular cysts.

The thymus, adrenals, mammary glands, pancreas and pituitary appeared normal. The thyroid microscopically showed a diffuse and focal dense connective tissue increase with hyalinization in some places and lymphocytic foci in others. The brain showed only an anomaly in the circle of Willis. Instead of a single anterior communicating artery joining the anterior cerebral arteries there was a network of arteries from which passed a single right anterior cerebral and two left anterior cerebral arteries, the latter communicating 1 cm. from their origin but still remaining separate trunks. The lymph nodes showed no changes except those mentioned with respect to the tracheobronchial nodes. The muscular system and skeleton likewise showed no abnormality. The bone marrow from a rib and from a lumbar vertebral body showed a hyperplasia of hemopoietic elements.

Anatomical Diagnoses: Multiple fibroleiomyomas of the uterus; multiple solid and cystic fibroleiomyomatous metastases to each lung and to the tracheobronchial lymph nodes; pulmonary emphysema and slight hyperemia; hypertrophy and dilatation of the heart, particularly of the right ventricle; generalized passive congestion; ascites; edema of the dependent parts of the body; parenchymatous degeneration of the liver and kidneys; petechial hemorrhages in the mucosa of the stomach, jejunum, ileum and colon; acute erosions of the duodenal mucosa; fibrous pleuritis; accessory spleens (2); and anomaly of the circle of Willis.

Essential Microscopic Features

Except for the tumors in the uterus, lungs and tracheobronchial lymph nodes, the microscopic changes have been briefly given and will not be repeated. Tissues were fixed in Zenker's and

Bouin's solutions and in formalin. Embedding was in paraffin and celloidin. Sections were stained by hematoxylin and eosin, phosphotungstic acid hematoxylin, Mallory's aniline blue stain for connective tissue, Van Gieson's connective tissue stain and Masson's trichrome method. The distribution and fate of the elastic tissue in the lung was studied by Weigert's method. Frozen sections of heart, liver and kidney were stained for fat. The autopsy was begun 3 hours and 20 minutes after death but all tissues were not fixed immediately so that the results of the differential staining were not perfect.

Uterus: Sections from sixteen locations in the uterine tumors show, except for minor differences, the same microscopic picture. The tumors resemble the common fibroleiomyoma with the smooth muscle component conspicuous (Fig. 9). In some areas the tumor is very vascular and in these places the cells tend to be shorter than elsewhere and to exhibit a tendency to a perivascular arrangement. Dense connective tissue stroma with much collagen is abundant in some nodules, while others show much edema fluid separating the tumor cells. Other degenerative changes, common in fibroids, except for the liquefaction necrosis seen in one tumor nodule, are absent. In one section made from the tumor which extended into the broad ligament superficial infiltration of tumor cells into skeletal muscle is noted although this had not been observed on gross dissection. Invasion of tumor cells through the wall of a uterine vein to form a sessile mass projecting into the circulating blood is seen in one section.

The predominant cytological constituent of the tumor is smooth muscle. Anaplasia is absent in the tumor cells. The nuclei are regular, symmetrical and cigar-shaped, and lie parallel. There are more nuclei per unit volume than are usually seen in proliferating tissues composed of young connective tissue, and the nuclei contain more chromatin than do young fibroblasts. Mitotic figures are rarely found. The cells form fascicles which interweave. Among the muscle cells are connective tissue cells, which are numerous in some areas. Mast cells are also scattered throughout the sections.

The stains for fibrillar cytoplasmic material show that there are myofibrils within tumor cells. They can be seen where the cells are cut transversely and they also appear where the cells are

cut longitudinally, although here their localization within the cytoplasm of the cells is less certain. The myofibrils, in many places, appear to be degenerating, being clumped near the nucleus and taking a reddish brown instead of a blue color with the phosphotungstic acid hematoxylin stain. Coarser myoglia fibrils, which stain blue to black with the same stain, are visible on the surfaces of the cells in many regions.

The chromatic properties of the tumor cells in the various stains, with respect to both the nucleus and the cytoplasm, are best compared with the blood vessel walls in the same sections. They are seen to resemble the smooth muscle cells of the tunica media and not the young fibroblasts of the tunica adventitia. The fibrils of the tumor cells have the tinctorial qualities of the elastic fibers of the blood vessel wall, where such are visible. Dense connective tissue with collagen is present in all sections. In some regions it is abundant while in the younger, perivascular regions very little is seen. The relationship and relative amounts of the various types of fibrils are easily seen in edematous regions where the cells have been teased far apart and conform essentially to the above descriptions.

Sections through the endometrium show an infiltration by plasma cells, lymphocytes and neutrophils, numerous thin walled blood vessels and an atrophic epithelium. The cervical glands are also atrophic. Numerous sections through the para-uterine vessels reveal many veins and one artery to be thrombosed by recent or by organizing thrombi not containing tumor at the levels studied.

Lung: Except for less vascularity and an even more highly differentiated cell morphology, the cytological appearance of the lung metastases resembles that seen in the uterine tumors. The essential tumor cells appear to be smooth muscle with a stroma of varying amounts of dense connective tissue. These cells form circumscribed but encapsulated infiltrative nodules, mainly in the interstitial regions, but also in the region of perivascular and peribronchial lymphatic channels (Figs. 6 and 7). Some nodules are composed of solid masses of tumor cells, but in the majority are also found irregular spaces lined by flattened or cuboidal epithelium resembling that seen in chronically scarred lung tissue. These spaces resemble persistent alveoli which have become lined

by cuboidal epithelium. Most of these alveoli are collapsed, with opposing epitheliums in contact, but others are open and appear to contain either air or mucus. The nature of the remarkable air cysts described in gross is revealed by studying the forms these alveoli assume. The cystic tumors appear to represent enormously enlarged alveolar sacs. Their walls are composed of smooth muscle tumor cells which are greatly elongated and they are lined by flattened epithelial cells. Solid and cystic lung tumors, therefore, differ only in whether an enlarging alveolus persisted within the tumor nodule. The large mucus-filled tumor mass found in the right lung has lining cells which appear to have formed the mucus. The presence of myofibrils and myoglia fibers can be demonstrated in the lung metastases (Fig. 8). No tumor growth is noted within large blood vessels in the lung.

Lymph Nodes: Fibroleiomyomatous tissue is seen in the peripheral sinus and in an afferent lymphatic of a lymph node removed from the region of the bifurcation of the trachea (Fig. 10). The cells here also appear fully differentiated and benign. The specific fibrils for smooth muscle are present. Fibrous stroma is present and the tumor tissue is relatively avascular.

Discussion

Several points in the clinical history are worthy of emphasis. Very striking was the clinical picture, which was that of pulmonary disease with obstruction to blood flow through the lungs, rather than that of pelvic neoplasm. The polycythemia, together with hypertrophy of the right ventricle, was effective in maintaining compensation for about a year, but the last 6 months of life were characterized by a progressive failure of the right side of the heart.

The long duration of the disease is also interesting and indicates that the rate of growth of the lung tumor metastases was slow, a fatal termination occurring after 18 months of illness. Since there was no great change in the X-ray films during the last year of life it is probable that the lung metastases had been present for a long time before they had attained a size and number sufficient to produce the first symptoms. The microscopic appearance of the tumor is likewise that commonly associated with slow growth.

Another striking feature was the marked disproportion between

the extent of the disease as indicated by the X-ray studies of the lungs and the degree of incapacitation of the patient. Her general condition was better than would be thought possible, and the rate of decline was slower than that accompanying the commoner lung infections or metastatic tumor to the lungs in which the X-ray signs are so advanced. The absence of regression of the tumor tissue in the lungs under X-ray therapy is in conformity with what is known about the radiosensitivity of this type of tumor.

The age of the patient is also interesting. Most uterine sarcomas occur near the menopause, while this patient was only 36 years of age.

Williams [11] was among the first to show that malignant uterine tumors may be derived from smooth muscle. Mallory [12, 13] gave staining procedures by which muscle cell tumors can be identified on the basis of their fibrils. Characteristic fibrils are present in this tumor so there is no question as to its fundamental myomatous nature.

It is generally recognized that there is no sharp point of differentiation between benign and malignant muscle cell tumors. The myosarcomas in general have less stroma and are therefore softer and fleshier. They tend to be more vascular and are unencapsulated and poorly demarcated. They are cellular, with changes in the nuclei varying from little change to extreme anaplasia. In general the nuclei are shorter, more chromatic, uneven in size and shape, and show an increased number of mitotic figures. The loss of normal nuclear structure is accompanied by loss of the characteristic cytoplasmic fibrils. Anaplasia may be so marked that the fundamental nature of a tumor, whether it originated from muscle cells or fibrous stroma, cannot be determined.

In the routine microscopic examination of surgically removed uterine fibroids not infrequently cellular tumors exhibiting some of the cytological features associated with malignancy mentioned above are encountered. In the recorded literature this incidence varies from a small fraction of 1 per cent to over 10 per cent. Corscaden and Stout have recently discussed this situation [14] and have pointed out the error in diagnosis by those who find the higher figures. In these tumors the cytological changes are sometimes misleading since in a series of untreated fibroids, or in a series treated lightly by X-rays, no corresponding high incidence

of fatal uterine sarcoma is found. Uterine sarcomas in general autopsy series are relatively uncommon. Kimbrough [15] found that the 5 year survivals were three times as great in so-called sarcomatous degeneration of fibroids as in the primary uterine sarcomas. Any errors in diagnosis would most likely have been in the first group.

Although it is a common experience to find suspiciously sarcomatous regions in uterine fibroids, which are clinically permanently benign, the case here reported is an example of a much rarer condition in which a tumor composed of benign appearing cells proved to be clinically malignant.

Since the usual cytological changes are frequently misleading in the diagnosis of malignant uterine tumors, more reliable criteria have been sought. The mitotic figure count as an index of malignancy is accepted as of value by many. Evans [16] in 1920 pointed out that the clinical malignancy closely follows the number of mitotic figures. Kimbrough,[15] Handley and Howkins,[17] and others, have found this procedure of value. Meigs [18] states that malignancy must be suspected if more than 1 or 2 mitotic figures are seen in 10 to 25 high power fields. Casey [19] has studied the number of mitotic figures per 1000 tumor cells in a variety of neoplasms and has found that in general benign tumors have fewer than 4 and malignant tumors more than 4 mitotic figures per 1000 tumor cells. In this respect also the tumor in our case is unusual in that the number of mitotic figures is not correlated with the clinical malignancy. In the uterine tumors (2000 cells), lung metastases (1000 cells), and lymph node metastases (1000 cells) no mitotic figures were encountered (autopsy material). Accordingly, by this criterion, this case falls into the group of benign tumors, and this is in agreement with its general microscopic morphology. Yet its known clinical behavior was that of a malignant tumor.

The routes of metastasis in this case were undoubtedly by the veins from the uterus to the lungs and through lymphatics from the lungs to the tracheal lymph node. Several theories have been proposed to explain how cells so harmless appearing might metastasize. Thus Proper and Simpson [20] state: "They are probably really benign and metastasize as the result of the cells of a leiomyoma penetrating a blood vessel and producing another

tumor at the place where these cells become lodged." Van Rijssel [21] and Sitzenfrey [22] believe that benign appearing tumor cells enter blood vessels by pressure atrophy of the vessel wall.

Nature of the Tumor: Grossly there was little to indicate that the tumors in the uterus were malignant or capable of producing metastases. The appearance was that of a uterus enlarged by common fibroids. The tumors were firm, reddish gray, silky and whorled in most places, and on the whole shelled out readily. Nowhere in the uterine tumors or in the metastases was the tumor tissue friable or fleshy like a sarcoma. In retrospect one feature in the gross appearance may be of the greatest importance in recognizing this type of tumor. Although the uterine tumors separate easily from the tissue in which they are embedded, *some of them are seen to be not globular but elongated and to have a little tendency to interweaving or intertwining of adjacent tumors — in other words, a plexiform growth.* In this respect it resembles the case of Lahm.[23]

Microscopically, although the appearance was that of fibroleiomyoma, two points in examination of the uterine sections reveal the possibility of metastases. The tumor cells were capable of invading veins and they were able to infiltrate striated muscle. Neither of these features had been noted grossly. They indicate an unexpected potentiality of the cells and clarify the mechanism of the metastases.

Microscopic sections from this case have been seen by about twenty experienced pathologists. A few of them commented on the unusual degree of vascularity of some, but not all, areas in the uterine tumors. Others said that this was of a degree not uncommon in fibroids. Small blood vessels are numerous in some places and the tumor cells immediately adjacent appear more immature than those at a distance. This vascularity is less striking in the lung metastases, being entirely absent in large portions, and it is not seen at all in the lymph node metastasis. So it appears not to be an essential part of the growth.

Could the tumor be one of a primary vascular growth? The fact that the tumor cells immediately about blood vessels are shorter, appear younger, and that there is less collagen speaks for more rapid growth in these regions. The tumor cannot be proved to have a vascular origin. In fact, the presence of adventitial cells

separating the media of the blood vessels from tumor cells in certain areas is evidence against such a hypothesis. Furthermore, a perivascular proliferation of tumor cells is no proof of a vascular origin, but it may rather indicate a more favorable environment for growth in the form of better nutrition, a feature commonly seen in carcinomas and other tumors.

Discussion of Nomenclature: I have no strong convictions about the nomenclature of this type of tumor and have used the descriptive term "metastasizing fibroleiomyoma" at the insistence of some oncologists who saw the sections, and to strengthen the teaching points of the case. I have refrained from using the word benign. The incongruity of the term is apparent and I appreciate that the clinical outcome of the case resembled that of a malignant tumor.

In the nomenclature of malignant mesenchymal uterine tumors, by usage the term "sarcoma," with some qualifying term such as leio-, fibro-, mixed cell, undifferentiated, and so on, is widely accepted. This is true aside from the question of their primary origin from myometrium or from a previous fibromyoma. The term "myoma malignum" has been used by some writers for tumors in which the microscopic appearance suggested a malignant tumor but in which definite proof of malignancy was wanting, a position not infrequently met with in the routine examination of surgically removed fibroids. This same term is also used by others in a different sense to describe those instances in which a fibroleiomyoma becomes frankly malignant. The term "sarcoma myomatoides" has an even more diversified usage, having been used to describe tumors of each of the above three types. So none of these terms is entirely applicable to this case. Strong [24] has reviewed the problem of nomenclature in considerable detail.

Casting aside for the moment the term I have used, what name would be most suitable? I do not say that this is not a sarcoma, but if it is, that diagnosis must be made on other grounds than tissue morphology. Shall we say sarcoma of the uterus, as did Jacquin,[25] even if the histological appearance is benign? To do this is an admission that the diagnosis of sarcoma from biopsy material before the final clinical outcome is known is impossible in some instances.

As broad criteria of malignancy the familiar qualities of neoplasia, heterotopia and anaplasia present themselves. Of neoplasia

there can be no question in this case, but it is a property shared by benign and malignant tumors alike. Heterotopia was also present but there was no evidence of anaplasia. Under these circumstances the term myoma malignum might be considered more appropriate for this case than metastasizing fibroid, except that, as pointed out, this term is used by some in instances where cell anaplasia is present. In dealing with epithelial tumors the term "adenoma malignum" is used by some when there is neoplasia, a minimal degree of anaplasia, and no proof of heterotopia. It is useful in transmitting from the pathologist to the clinician the idea that the tumor is probably malignant but not so proved. In the present case the tumor was clinically malignant because of heterotopic muscle cells. McFarland [26] concludes that metastasis is the only proof of malignancy in dealing with muscle tumors. But benign fibroleiomyoma cells are capable of growing ectopically under special circumstances as shown by Brewer's [27] case in which cells from uterine fibroids, implanted into the abdominal wall, grew.

The problem as to nomenclature is not an important one since the question does not often arise.

Review of the Literature

A. Metastasizing Fibromyomas of the Uterus: A critical comparison of our case with those previously reported is extremely difficult because the earlier papers are not illustrated or are inadequately illustrated, histological descriptions are absent or sketchy, and there is considerable confusion in the nomenclature. Undoubtedly other cases have been overlooked, but the following 4 cases summarize those found in a fairly careful survey of the literature. Some of these cases are without description or illustration.

The 1st case reported was that of Krische [28] in 1889, in which fibromyomas of the uterus metastasized to many parts of the body. There was said to be abundant fibrous stroma. Orth [29] accepts this case as one of metastasizing fibroids without comment. Meyer,[3] however, refuses to accept this case, stating that its sarcomatous nature is firmly established.

The 2nd case of this type was reported by Langerhans [30] in 1893. It was that of a 60 year old woman who had multiple tumor

nodules in the uterus. One of these was predominantly smooth muscle, another was pure smooth muscle and the rest were fibromyomas. There were multiple pulmonary metastases composed of cells which were larger and more irregular than those in the uterus. There was, therefore, some change from normal smooth muscle structure (anaplasia) in the lung, the degree of which cannot be estimated because the paper is not illustrated. He called it a "myoma laevicellulare malignum."

The 3rd case on record is that of Minkowski,[31] who in 1901 at autopsy found metastases composed of adult smooth muscle but lacking all stroma, in the lungs, liver and muscles of a 43 year old woman who 2 years before had had a complete hysterectomy for a "fibromyoma" of the uterus. There are no illustrations or detailed descriptions, the case having been presented briefly before the medical society at Köln. He gave it the name of metastatic myoma.

The 4th case was that which Schlagenhaufer[32] reported in 1902. A woman, 58 years of age, had multiple uterine tumors with metastases to the liver and lungs. Microscopically part of the uterine masses were typical fibromyoma while others were composed of muscle cells exclusively and had many large and small blood vessels, giving a cavernous appearance. There was no fibrous stroma. Some of the muscle cells showed anaplasia, being large and having multiple nuclei. In the metastases the vascular cavernous structure was not seen. The drawing which accompanied this report illustrates pure smooth muscle of a well differentiated type. He called his case "myoma telangiectodes."

Of these cases those of Langerhans and Schlagenhaufer can be discarded from this group, since, by their own descriptions, the tumor cells showed a certain degree of anaplasia. Schlagenhaufer was impressed by the vascularity of his tumor. His paper, alone, is illustrated. Minkowsky and Schlagenhaufer thought that the absence of stroma (binding-substance) explained the malignant behavior of their tumors. Only the case of Krische had stroma.

In addition to these case reports of benign appearing metastasizing tumors of the uterus the literature contains references to such occurrences without presenting the details. Thus, Lockyer[33] states: "In common with other observers, I have examined the metastatic deposits from the lungs and pelvic cellular tissues of a

case in which there was a large myoma of the uterus, and where all the growths, primary and secondary, had the structure of an innocent-looking myoma. Unfortunately the specimen, which was removed by the late Stanley Boyd, had been lost, but the sections are preserved, and the lesson they teach suffices to obliterate any suspicion I may have had as to such a condition being a fact."

Also McFarland [26] in speaking of myomas in general, including those from the uterus, states, without giving details of such cases: "Histopathologic prognosis is fraught with difficulty. We have all seen, on the one hand, the tumor whose histological structure appeared to be that of an ordinary fibroid, accompanied by one or more metastases of identical appearance, and on the other, a tumor of the most suspicious appearance whose history has terminated with its removal."

Kaufmann,[6] also without citing a case, writes: "Malignant myomas produce metastases by the blood channels, possibly through the lymphatics also; therefore biologically, according to their growth, they are malignant, but histologically they are typical myomas, distinguished from sarcomatous myomas in that their muscle cells are more uniform and of higher development."

Not available to the writer is the volume in which Johnstone (according to Lockyer [34]) mentions 10 cases in which pulmonary and other metastases showed a structure of unstriped, benign appearing muscle tissue.

B. Recurring Fibromyomas of the Uterus: In discussions of this subject, the cases which von Franqué [35] reported in 1907 and which Jacquin [25] described in 1921 are usually included. They are examples, not of metastasizing but of recurring fibroleiomyomas. The case of Jacquin showed a microscopically benign recurrence 10 months after a hysterectomy for benign fibromyoma. The patient of von Franqué was even more interesting because of three recurrences over a period of 7 years. The tumors showed pure myoma with very little connective tissue, and areas of edema and of hyaline degeneration. The muscle of the vessel walls was not demarcated from tumor in some places.

More recently Neugebauer [36] in 1927 briefly reported an instance in which 6 years after supravaginal hysterectomy for benign myoma there were found three pelvic tumors entirely

separated from the amputation area and all showing the histological structures of simple benign myoma. This paper is without illustration or detailed histological report.

Christophorakos [37] described the case of a fibromyoma of the uterus in which there were three recurrences in 3 years, the first two of which appeared like benign myomas, while the third showed areas of pleomorphic sarcoma in addition to myoma. Matthews and Stier [38] saw a patient who died of a fourth recurrence and distant metastases about 10 years after a uterus with multiple fibromyomas was removed. The recurrences showed progressive deviation from normal, the first recurrence appearing benign and the last like a spindle celled sarcoma.

These cases of Christophorakos and of Matthews and Stier raise the question as to whether the other foregoing tumors would have changed their morphology to frank sarcoma if they had recurred again several times.

C. Intravascular Uterine Fibromyomas: In addition to the groups of metastasizing fibromyomas and recurring fibromyomas mentioned above, a third group of cases sheds light on this subject. This includes cases in which uterine fibromyomas extended into the regional blood or lymph vessels, yet failed to metastasize. They are of special interest in this connection because they may be illustrations of the early stages of the type of metastasis seen in the case here reported. Birch-Hirschfeld [39] (3 cases) and Meyer [40] described tumors with intralymphatic extensions. Von Franqué,[35] Hörmann,[41] Dürck,[42] van Rijssel [21] (2 cases), Seyler,[43] and Sitzenfrey [22] (3 cases) reported cases with intravenous growth. Lahm's [23] case was unique in showing both lymphatic and venous growth, although he saw changes at least suspicious of malignancy.

In this connection the report of Frank [44] should be kept in mind. He described 3 cases of plexiform growth within the lymphatics of the myometrium by a tissue which resembled endometrial stroma.

Summary

A case is reported in which multiple tumor metastases to the lungs from the uterus led to chronic obstruction to blood flow through the lungs, polycythemia, enlargement of the right side of the heart, and finally to heart failure. The uterine tumors micro-

scopically appeared to be benign fibromyomas with areas that were quite vascular. The lung and tracheal lymph node metastases appeared even more mature and benign. In the absence of changes in color and consistence, local invasion of veins or rapid growth, uterine tumors which resemble fibroids but have a little tendency to plexiform growth should be considered potentially malignant. No new microscopic criteria have been discovered by which the malignancy of such cases can be recognized in the future. The mitotic figure count on postmortem specimens was non-informing as to the malignancy. The tumor in our case was histologically benign appearing, but clinically malignant. Such cases are much rarer than those in which histologically malignant appearing uterine tumors (cellular myomas) prove to be clinically benign. Four cases of metastasizing uterine fibromyomas reported previously, 2 of which, however, showed signs of malignancy, are briefly summarized.

REFERENCES

1. Ewing, James. Neoplastic Diseases. A Treatise on Tumors. W. B. Saunders Company, Philadelphia, 1928, Ed. 3, 223.
2. Stout, Arthur Purdy. Human Cancer. Lea and Febiger, Philadelphia, 1932, 335.
3. Meyer, Robert. Metastasierung histologisch einfacher Myome. Handbuch der Gynäkologie, Veit, J., and Stoeckel, W. J. F. Bergmann, Munchen, 1930, Ed. 3, **6**, 308.
4. Albrecht, Hans. Pathologische Anatomie und Klinik des Uterussarkoms. Sarcome myocellulare, muskelzelliges Sarkom. Biologie und Pathologie des Weibes, Halban, Josef, und Seitz, Ludwig. Urban and Schwarzenberg, Berlin, 1928, **4**, 611.
5. Raab, Heinrich. Zellreiche Myome und Myosarkome des Uterus. *Arch. f. Gynäk.*, 1913, 100, 389–429.
6. Kaufmann, Edward. Pathology for Students and Practitioners. Translated by Reimann, Stanley P. P. Blakiston's Son and Company, Philadelphia, 1929, **3**, 1666.
7. Borst, M. Echte Geschwülste (Gewächse, Blastome). Pathologische Anatomie. Ein Lehrbuch für Studierende und Ärzte, Aschoff, L. Gustav Fischer, Jena, 1928, Ed. 7, **1**, 738–739.
8. Aschoff, L. Weiblicher Geschlectsapparat. Pathologische Anatomie. Ein Lehrbuch für Studierende und Ärzte. Gustav Fischer, Jena, 1928, Ed. 7, **2**, Chapt. XI, 610–612.
9. Wolff, Jacob. Metastasen gutartiger Geschwülste. Die Lehre von der Krebskrankheit. Gustav Fischer, Jena, 1911, **2**, 403–406.

10. Ribbert, Moritz Wilhelm Hugo. Geschwulstlehre für Aerzte Studierende. Friedrich Cohen, Bonn, 1914, Ed. 2, 432.

11. Williams, J. Whitridge. Contributions to the histology and histogenesis of sarcoma of the uterus. *Am. J. Obst.*, 1894, **29**, 721–764.

12. Mallory, F. B. A contribution to the classification of tumors. *J. M. Research*, 1905, **13**, 113–136.

13. Mallory, F. B. The results of the application of special histological methods to the study of tumors. *J. Exper. Med.*, 1908, **10**, 575–593.

14. Corscaden, J. A., and Stout, A. P. Sarcoma of the uterus. *Am. J. Roentgenol.*, 1929, **21**, 155–167.

15. Kimbrough, Robert A., Jr. Sarcoma of the uterus: factors influencing the results of treatment. *Am. J. Obst. & Gynec.*, 1934, **28**, 723–730.

16. Evans, Newton. Malignant myomata and related tumors of the uterus; report of 72 cases occurring in a series of 4,000 operations for uterine fibromyomata. *Surg., Gynec. & Obst.*, 1920, **30**, 225–239.

17. Handley, R. S., and Howkins, J. Sarcoma of the uterus. *Lancet*, 1937, **2**, 1180–1184, 1246–1250.

18. Meigs, Joe Vincent. Tumors of the Female Pelvic Organs. The Macmillan Company, New York, 1934, 149.

19. Casey, Albert E. Studies on the mitosis rate in tumors of several mammalian species. *Am. J. Path.*, 1937, **11**, 886–888.

20. Proper, Mina Shepard, and Simpson, Burton T. Malignant leiomyomata. *Surg., Gynec. & Obst.*, 1919, **29**, 39–44.

21. Van Rijssel, E. C. Metastaseering van gezwellen. *Nederl. tijdschr. v. geneesk.*, 1930, **74**, 720–729.

22. Sitzenfrey, Anton. Ueber Venenmyome des Uterus mit intravaskulärem Wachstum. *Ztschr. f. Geburtsh. u. Gynäk.*, 1911, **68**, 1–25.

23. Lahm, W. Zur Frage des malignen Uterusmyoms. *Ztschr. f. Geburtsh. u. Gynäk.*, 1915, **77**, 340–347.

24. Strong, Lawrence W. The morphology and histogenesis of stromatogenous uterine neoplasms. *Am. J. Obst.*, 1915, **71**, 230–248.

25. Jacquin, P. À propos du sarcome et myome malin de l'utérus. *Gynéc. et obst.*, 1921, **3**, 90–111.

26. McFarland, Joseph. Malignant myoma. *Am. J. Cancer*, 1935, **25**, 530–543.

27. Brewer, George Emerson. Typical fibromyoma of the abdominal wall following hysterectomy. *Ann. Surg.*, 1921, **74**, 364–367.

28. Krische, Georg. Ein Fall von Fibromyom des Uterus mit multiplen Metastasen bei einer Geisteskranken. Diss. Göttingen, W. F. Kästner, 1889.

29. Orth, Johannes. Lehrbuch der speciellen pathologischen Anatomie. August Hirschwald, Berlin, 1893, **2**, Pt. 1.

30. Langerhans, R. Demonstration eines Präparates von Myoma laevicellulare malignum. *Berl. klin. Wchnschr.*, 1893, **30**, 338–340.

31. Minkowski. Myommetastasen in Lungen, Leber, und Muskeln. *München. med. Wchnschr.*, 1901, **48**, 1335.

32. Schlagenhaufer, Friedrich. Myoma teleangiectodes uteri mit reinen myommetastasen in der Leber und den Lungen. *Wien. klin. Wchnschr.*, 1902, **15**, 523–525.

33. Lockyer, Cuthbert. Fibroids and Allied Tumours. The Macmillan Company, Ltd., London, 1918, 83–84.

34. Eden, Thomas Watts, and Lockyer, Cuthbert. The New System of Gynaecology. The Macmillan Company, London, 1917.

35. Von Franqué, Otto. Über Myoma sarcomatodes parametrii und Myoma malignum parametrii post Myoma malignum uteri. Festschrift für Georg Eduard von Rindfleisch, Borst, Max. Wilhelm Engelmann, Leipzig, 1907, 29–42.

36. Neugebauer, Friedrich. Freie Myome im Beckenbindegewebe nach supravaginaler Amputation des myomatösen Uterus. *Zentralbl. f. Gynäk.*, 1927, **51**, 99–102.

37. Christophorakos, Nikolaus. Metastasen von wechselnden Geschwulstcharakter bei Myosarkom des Uterus. *Zentralbl. f. Gynäk.*, 1933, **57**, 1935–1940.

38. Matthews, A. A., and Stier, R. F. Progressive change of myofibroma to spindle cell sarcoma. *Western J. Surg.*, 1935, **43**, 40–46.

39. Birch-Hirschfeld, Felix Victor. Lehrbuch der pathologischen Anatomie. F. C. W. Vogel, Leipzig, 1896, Ed. 5.

40. Meyer, Robert. Zur Pathologie der Myome, insbesondere über ihr Wachstum und ihre Histogenese. *Zentralbl. f. Gynäk.*, 1907, **31**, 1244–1245.

41. Hörmann, Karl. Über einen Fall von myomatösem Uterustumor. (Demonstration.) *Zentralbl. f. Gynäk.*, 1907, **31**, 1604–1605.

42. Dürck. Ueber ein kontinuierlich durch die untere Hohlvene in das Herz vorwachsendes Fibromyom des Uterus. *München. med. Wchnschr.*, 1907, **54**, 1154.

43. Seyler. Histologisch typische und homologe Myome des Uterus mit "intravenösem" Wachstum. *Virchows Arch. f. path. Anat.*, 1921, **233**, 277–285.

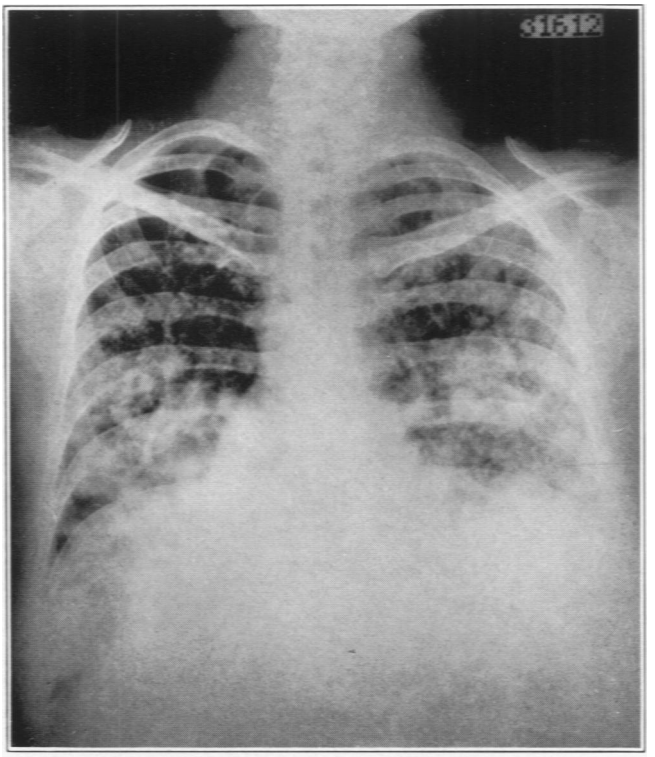
44. Frank, Robert T. "Fibromyosis": An unclassified plexiform endolymphatic proliferation of the uterus, with report of three cases. *Am. J. Cancer*, 1932, **16**, 1326–1336.

DESCRIPTION OF PLATES

PLATE 21

FIG. 1. X-ray of chest made about a week before death. A similar degree of involvement was present a year earlier. The picture is not like that usually produced by tumor metastases to the lungs.

FIG. 2. X-ray of the excised inflated lungs. The solid and the cystic nodules can both be seen, the latter particularly at the margin. The heart is still attached. The large tumor metastasis is in the right lung.



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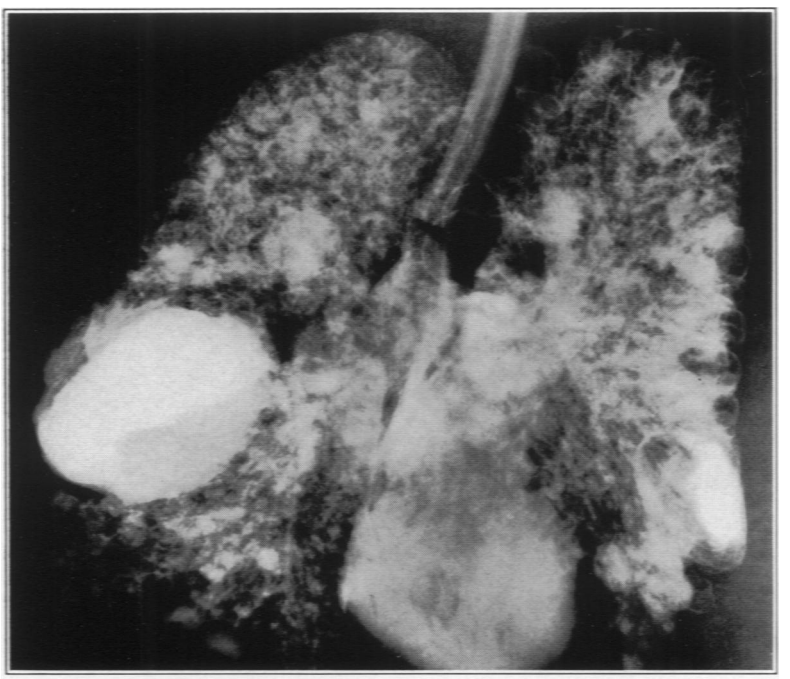


2

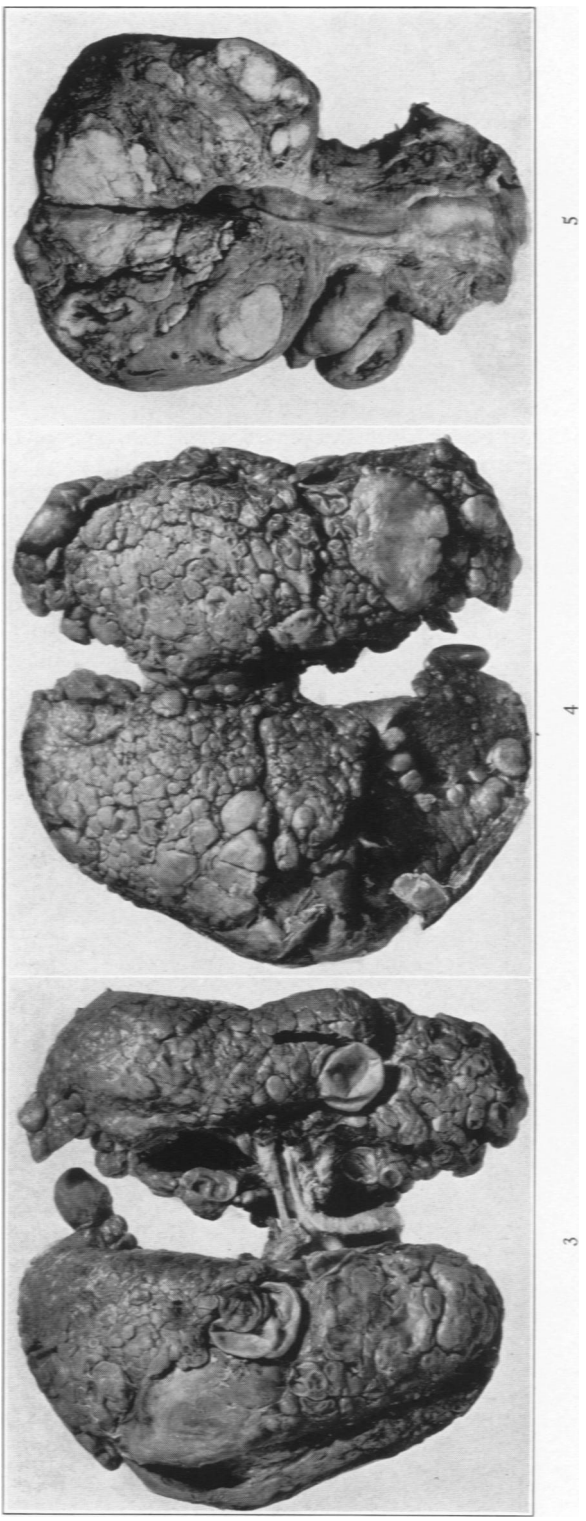
Steiner Metastasizing Fibroleiomyoma of Uterus

PLATE 22

FIG. 3. Posterior view of the lungs. The largest tumor mass is in the right lung. Pedunculated metastases can be seen at the margin.

FIG. 4. Anterior view of the lungs. Some tumor nodules are solid and others are air-containing with walls containing fibromyomatous tissue.

FIG. 5. Uterus. From below upward are seen the vagina, cervical canal and uterine cavity. Numerous tumor nodules occupy the anterior and upper uterine walls, and several nodules extend out into the right broad ligament.



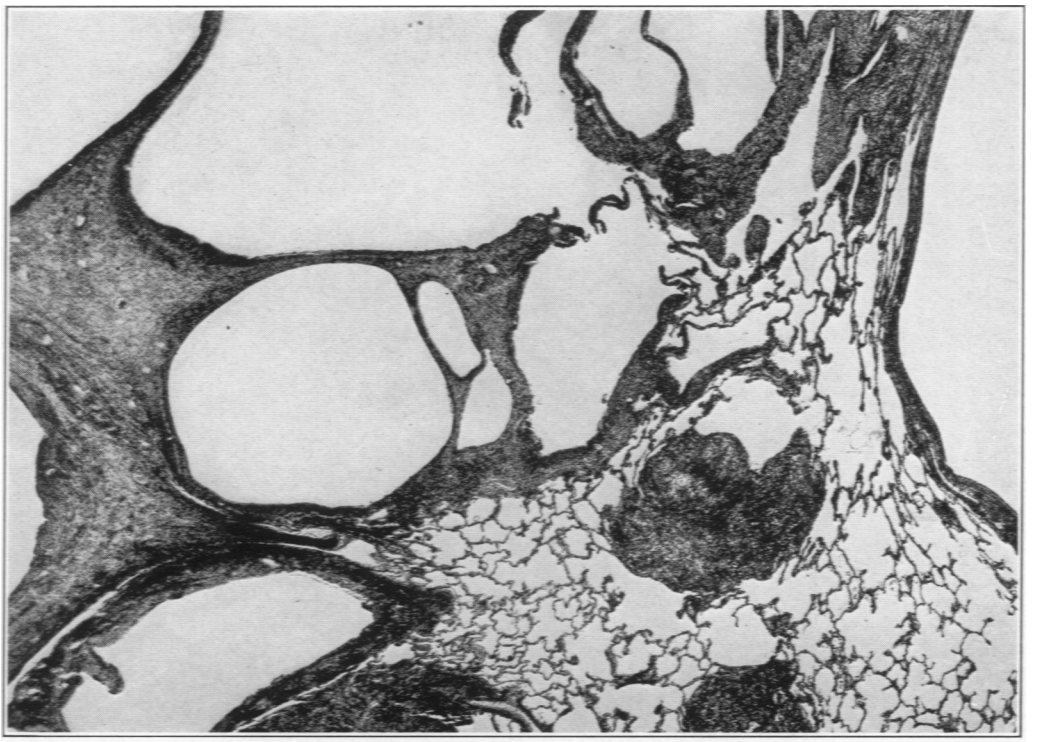
Steiner Metastasizing Fibroleiomyoma of Uterus

PLATE 23

FIG. 6. Section showing metastases to lung. The walls of the cystic tumor nodules are composed of smooth muscle lined by epithelium. A small, solid tumor metastasis is also shown. Only small areas of aerated lung resembling that illustrated are present in both lungs. × 10.

FIG. 7. Section showing the myomatous nature of the metastases to the lung. Hematoxylin-eosin stain. × 650.

FIG. 8. Section of metastasis to lung illustrating myoglia fibrils and myofibrils in cross and longitudinal section. Phosphotungstic acid hematoxylin stain. × 2600.



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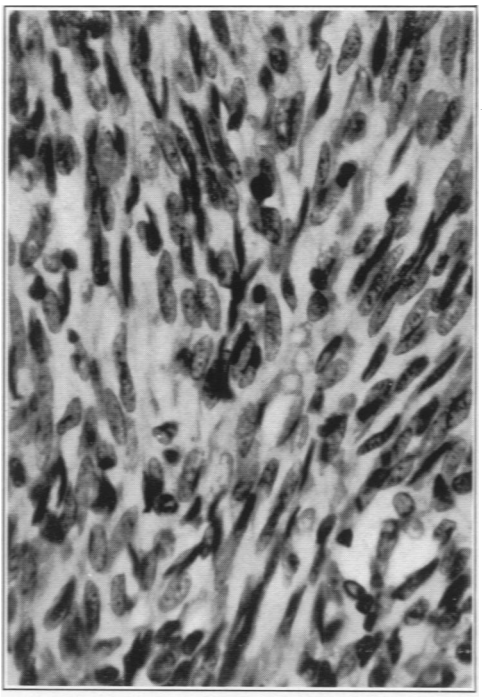

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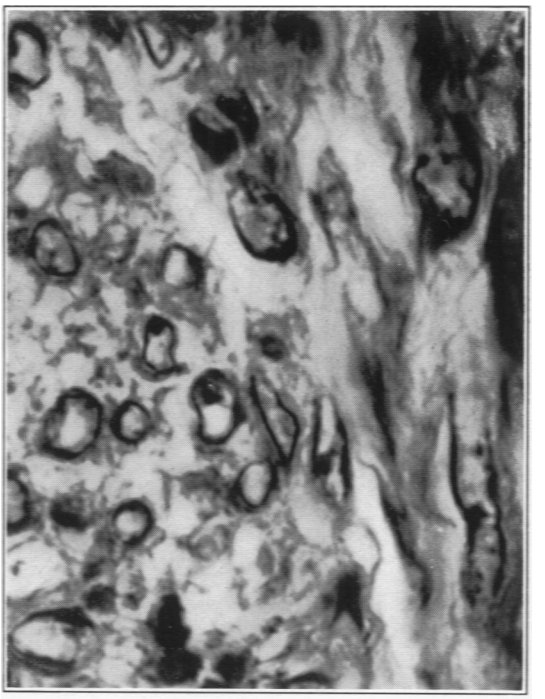

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Steiner

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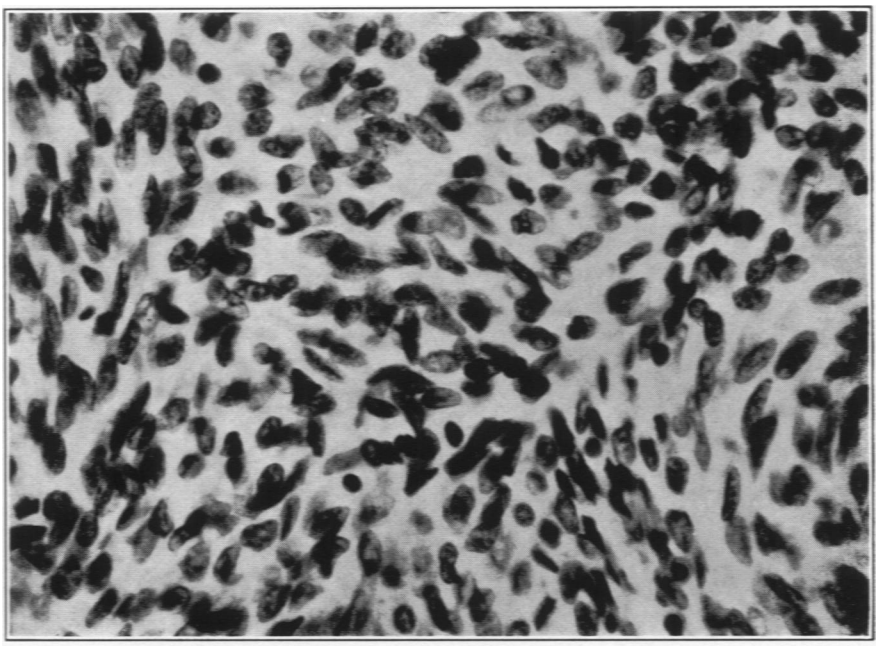
PLATE 24

FIG. 9. Section of a cellular area in the uterine tumor. Many of the cells are transected. Areas more suspicious than this were not seen. Hematoxylin-eosin stain. × 700.

FIG. 10. Metastasis in the peripheral sinus of a tracheal lymph node. The fully differentiated myomatous nature of the tumor is easily seen. × 550.



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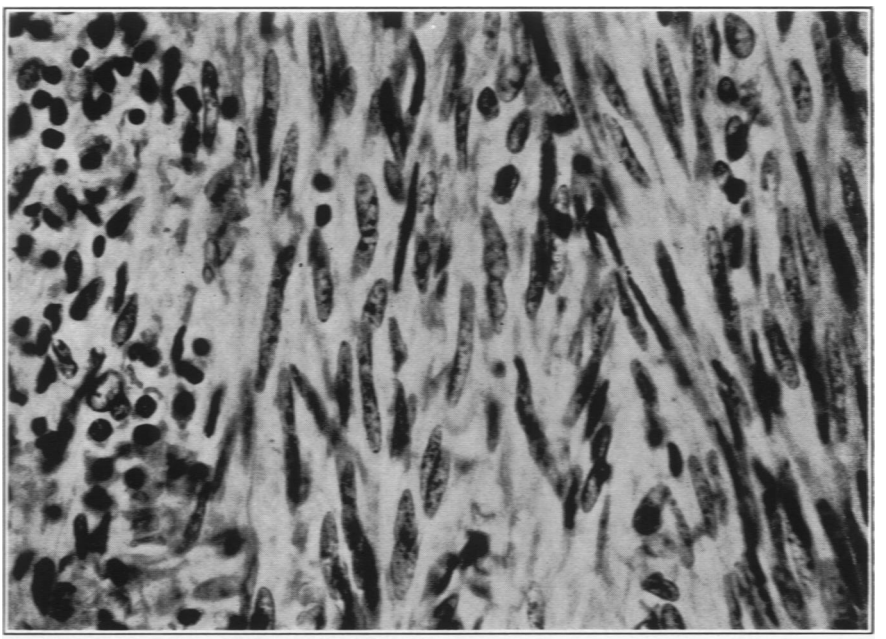

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