MALIGNANT MYOMA

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In an attempt to bring a greater degree of order out of the confusion surrounding the subject of malignant tumors of unstriated muscular tissue, 53 cases have been assembled. Twenty-four of these cases are taken from the author's private collection, and notes and material on 29 others were collected by Dr. Olga Leary from laboratories in Philadelphia and Boston. Dr. Leary also studied the literature, reviewing 69 articles before she was obliged to abandon this work to assume other duties elsewhere. The author takes this opportunity of expressing his indebtedness to her. While this seems a promising beginning, a really scientific study based on this series is precluded by the lack of adequate data on the individual cases. Of the 53 patients, only 16 had died of the tumor, and only 13 necropsies had been performed; of the patients known to be living, only one had shown signs of metastasis. There were, in fact, 34 cases, from various hospitals, in which the diagnosis of malignant myoma, leiomyosarcoma, or sarcomatous change in a leiomyoma had been made solely upon the microscopic appearances of the tumors, without any clinical confirmation. Whether the presence of identical or highly similar histological appearances in the 13 tumors shown by recurrence and metastasis to have been malignant, and in the 34 others concerning the clinical outcome of which nothing is known, can be regarded as sufficient to stamp the latter as malignant is a question.

The published writings upon the subject do not solve the problem. In them the same difficulty obtains. The chief criterion of malignancy is the histologic appearance of the tumor, and in a general way it may be said that where the greatest number of "fibroids" are most meticulously studied microscopically, the higher is the number of "malignant cases" recorded.

Cohen carefully reviewed 18,077 necropsies performed in eleven years at the Philadelphia General Hospital. Excluding the "uterine fibroids," he found only two malignant metastatic leiomyomatous tumors, one primary in the uterus with metastases to the lungs and liver, the other in the left kidney, with metastases to the lungs, right kidney, suprarenal glands, ileum, mediastinal and mesenteric lymph nodes, and brain.

Albrecht, compiling statistics from all available sources, estimated that 1.41 per cent of 77,076 uterine leiomyomas were malignant. The following figures (Table I) collected by Dr. Leary show that in the experience or opinion of different authors, the incidence of malignancy in leiomyomas of the uterus varies from zero to 10.0 per cent. Such a
discrepancy is beyond explanation except upon the supposition that he who found 10 per cent of the tumors to be malignant must have based his conclusions upon very different considerations from those employed by him who found none.

**Table I: Frequency of Malignant Change in Leiomyoma according to Different Authorities**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Myomas</th>
<th>Number Malignant</th>
<th>Percentage Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braun</td>
<td>1,760</td>
<td>7</td>
<td>0.4%</td>
</tr>
<tr>
<td>Fehling</td>
<td>409</td>
<td>8</td>
<td>1.9%</td>
</tr>
<tr>
<td>Fleichmann</td>
<td>19,620</td>
<td>24 histologically malignant</td>
<td>1.35%</td>
</tr>
<tr>
<td>Gardner</td>
<td>827</td>
<td>24 histologically malignant</td>
<td>2.9%</td>
</tr>
<tr>
<td>Geschickter</td>
<td>5,900</td>
<td>54</td>
<td>0.9%</td>
</tr>
<tr>
<td>Gieszen Clinic</td>
<td></td>
<td></td>
<td>6.0%</td>
</tr>
<tr>
<td>Geist</td>
<td>250</td>
<td>12</td>
<td>4.8%</td>
</tr>
<tr>
<td>Hertel</td>
<td>1,400</td>
<td>17</td>
<td>1.2%</td>
</tr>
<tr>
<td>Kelly and Cullen</td>
<td>2,274</td>
<td>17</td>
<td>1.2%</td>
</tr>
<tr>
<td>Kelly and Noble</td>
<td>1,518</td>
<td>17</td>
<td>1.1%</td>
</tr>
<tr>
<td>Lewis</td>
<td>4,322</td>
<td>4</td>
<td>0.9%</td>
</tr>
<tr>
<td>Miller</td>
<td>9,750</td>
<td>4</td>
<td>0.4%</td>
</tr>
<tr>
<td>Noble</td>
<td>337</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>Olshausen</td>
<td>6,470</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>Pfannenstiel</td>
<td>1,000</td>
<td>22 sarcomas</td>
<td>6.0%</td>
</tr>
<tr>
<td>Proper and Simpson</td>
<td>357</td>
<td>11 sarcomas</td>
<td>3.2%</td>
</tr>
<tr>
<td>Reel and Charlton</td>
<td>290</td>
<td>4</td>
<td>1.4%</td>
</tr>
<tr>
<td>Strong</td>
<td>306</td>
<td></td>
<td>3.8%</td>
</tr>
<tr>
<td>Udderström</td>
<td>789</td>
<td>15</td>
<td>1.95%</td>
</tr>
<tr>
<td>Voght</td>
<td>1,216</td>
<td>30</td>
<td>2.47%</td>
</tr>
<tr>
<td>Winter</td>
<td>500</td>
<td></td>
<td>3.2%</td>
</tr>
<tr>
<td>Winter</td>
<td>253</td>
<td></td>
<td>4.3%</td>
</tr>
<tr>
<td>Warnekros</td>
<td>78</td>
<td></td>
<td>10.0%</td>
</tr>
</tbody>
</table>

These reports have to do with uterine tumors, though they include a few of the ovary, fallopian tubes, and vaginal wall. But malignant myomas are by no means exclusively uterine or genital; they may occur wherever there are leiomyomas, and are possible wherever unstriated muscle tissue is to be found. In glancing over the literature, one finds the tumors—benign or malignant—reported as occurring in the following extra-uterine sites:

**Esophagus**
- Bezza
- Dvorak
- Papo and Spitznagel

**Stomach**
- D'Aunoy and Zoeller
- Antonow
- Cohen
- Edwards and Wright
- Geschickter
- Melnik
- Schiff and Foulger
Duodenum
Anderson and Doob
Case from author's collection

Jejunum
Cattell and Woodbridge

Ileum
Cohen

Cecum
Neugebauer
Trygstad

Rectum
Klages
Mornet and Delorme
Pohl
Rankin and Larson

Gallbladder
Krasbev (unpublished)
Case from author's collection

Kidney
Cohen
Crosbie and Pinkerton
Geschickter

Bladder
Krauskopf
Kretschmar
Caylor and Walters
Geschickter
Case from author's collection (Bothe)

Prostate
Costa
Geschickter
Harrison
Hinman and Sullivan

Labium majus
Silva

Ovary
Geschickter

Serosum
Cooney

Vagina
Schilling
Geschickter

Pleura
Catron

Retroperitoneum
Two cases from author's personal collection

Mesentery
Case of Dr. Konzelman, Temple University Hospital (specimens seen by author)

Skin
Ormsby

Breast
Abramow (a leiomyoma that may have had its origin in the unstriated muscle of the nipple and areola)

No cases seem as yet to have been reported from the iris, ciliary body, bronchial tubes, pancreatic ducts, or spleen, all of which contain at least a few unstriated muscle cells.
The observed distribution is so widespread as to have led to the suspicion that the tumors arise from the muscle in the walls of the blood vessels, rather than from that of the organs in which they appear. This conception is sponsored by Grynfeltt, Kleinwachter and Roesger, Grynfeltt going to the extreme of believing that even the common uterine tumors are of this origin. He says: "The myometrium is nothing but an enormous coalescing vascular trunk, and one might conclude that the origin of the tumor is from the same." Blood vessels, however, occur everywhere and the tumors only where there are other sources of unstriated muscle than the vessel walls.

Fig. 1. Malignant Leiomyoma of Duodenum with Fatal Recurrence Thirteen Years After Operation (Case of Dr. Baxter. L. Crawford). \( \times 200 \)

Small cells, few mitoses, few nuclear deformities, and scarcely a giant cell in the entire section.

It is now generally conceded that the uterine leiomyomas are dyson-togenetic tumors that arise from residual embryonal cellular material, as first suggested by Cohnheim. What is true of the uterine tumors is probably also true of others. If this view is correct, two controversial points may be dropped, first that which has to do with the power of fully developed and completely specialized unstriated muscle to multiply and produce tumors, and second that which seeks to explain the formation of the muscle through metaplasia of fibroblasts, or its evolution from lymphocytes, histiocytes, myoblasts, etc.

With respect to both of these theories there has been much publication by reputable authorities, but little convincing evidence. Fully
developed and completely specialized unstriated muscle appears to be incapable of multiplication, as the number of mitoses found in its cells is so small as to be negligible, and its capacity to regenerate after injury is insignificant. During the great increase in the volume of the myometrium during pregnancy, there is an enormous increase in the size of the cells, but very little if any increase in their number. Increase in number, if it does occur, is believed by Stieve to depend upon the appearance of entirely new "complementary" cells, developed for the emergency from latent embryonal cells, and in this he is supported by Schröder, who thinks that the myometrial cells proper atrophy to the normal size during involution, while these complementary cells disappear altogether. It goes without saying that during the evolution and multiplication of the complementary cells, and before they attain their specialization, any number of mitotic divisions may occur in them, and confuse the observer into believing that he sees myometrium itself in mitosis.

The common absence of mitotic figures in the gravid myometrium, and in leiomyoma, has led many, as, for example, E. B. Wilson, Plaut, Oertel, Peters, Palugyay and Ewing, to suppose that amitosis is the type of multiplication. But would it not be strange for the same cells to have two methods of reproduction and divide either with or without mitotic adjustments? In some of the muscle tumors mitoses are abundant; in others there are almost none at all. The difference may be better explained by assuming that those cases without mitoses are either inactive or mature than that they have adopted the amitotic form of cell division.

Maximow and Bloom, supported by Stieve, assert that "some of the smooth muscle cells which develop in the uterus during pregnancy, arise from the undifferentiated connective-tissue cells already present in this tissue, as well as from lymphocytes which wander into the myometrium in the early stage of gestation." Maximow also speaks of "the perivascular embryonic cells of the adult." If by the latter be meant latent embryonal tissue, this is in accord with the view of the writer; if, on the other hand, the reference is to the succession of transformations and metaplasias by which lymphocytes are assumed to wander out of the blood vessels, develop into histiocytes, and then become transformed into muscle cells, that is quite a different matter.

It seems, therefore, that the cells of the perfected myometrium do not multiply, but that among them are inactive or latent embryonic cells that assist its evolution in pregnancy, and which, under the stress of abnormal conditions or the influence of abnormal stimuli, may develop into tumors. Ribbert believed that he had seen deposits of such cells and says: "One may occasionally see the anlage of a myoma in the myometrium and recognize it by the darker staining of its closely compacted cells of small size, scant cytoplasm and short oval nuclei. Such anlagen have sharp borders and are packed into lacunae between the muscle bundles." In this he may or may not have been correct, but whether he saw them or not does not matter, the cells may have
been there just the same, and Cohnheim did not suppose it possible to identify them if seen. Leopold also thought that he had found the rudiments of myomas in the uteri of children.

Assuming that the source of the tumor may now have been satisfactorily accounted for, the next question of importance refers to its malignancy. Is it or does it become malignant, and if so, how and why? There might be no difficulty had we not become accustomed to the expression "becomes malignant." It seems highly probable that those tumors that turn out to be malignant are so from the beginning. Ewing answers the question when he says: "It is not to be assumed

This paper, though entitled "Malignant Myoma," is limited to tumors of unstriated muscle. It should perhaps have been called "Malignant Leiomyoma" or "Leiomyosarcoma." Here the difficulty of satisfactory nomenclature presents itself. What shall these tumors be called? Can a tumor made up of muscle cells be a sarcoma? Ribbert has protested against the employment of the term leiomyosarcoma, but Ewing thinks it justifiable. Exactly what is the tumor—or per-

**Fig. 2. Metastasis in the Neck, from a Malignant Uterine Myoma (Case of Dr. Jonathan Wainwright).** × 200

Large cells, mitotic figures, nuclear deformities, no giant cells. Although there were two other metastatic tumors, removed surgically, the patient was alive twelve years after hysterectomy.
haps more correctly the tumors—under consideration? Theoretically it should be a simple blastoma made up of cells representing some stage in the development of unstriated muscle tissue, and its degree of malignancy should correspond to the embryonal or adult state of its cells. One would suppose it easy to identify, but as a matter of fact it is so difficult that the term has come to include a number of different lesions, as follows:

(1) Tumors made up of undoubted muscle cells, all of which are uniformly large, with blunt ends, and oval vesicular nuclei, many of which are in mitosis.

(2) Tumors composed chiefly of completely differentiated muscle, almost identical in appearance with the myometrium, but in which, pushing apart the fasciculi of the original cells, are other fasciculi of embryonal cells like those mentioned above.

(3) Tumors in which fasciculi of perfected or embryonal muscle cells are separated and sometimes invaded and infiltrated by a different and smaller type of spindle cell, apparently unrelated to the muscle that it invades. In some parts of these tumors the cells, both invading and invaded, cease to cling together in fasciculi, shorten and become deformed, until great areas are made up of a miscellany of cells of all sizes and shapes with malformed and multiple nuclei.

(4) Tumors that occur as nodules in the myometrium or as smaller nodules in the leiomyomas of the myometrium, composed of fasciculi of short spindle-shaped (sometimes rounded) cells that show no indication of any relationship to the muscular tissue in which they occur.

The first of these four types may represent muscle cells uniformly growing and regularly multiplying to form a benign tumor; the second, a tumor, parts of which have fully matured while others continue to grow, or into whose finished substance a new invasion of embryonal cells is taking place. Such tumors are ambiguous. If the cells all mature, they are benign; if they do not and there is rapid proliferation of the embryonal cells, they may be malignant. In types 3 and 4 conditions are entirely different, for new cells, closely resembling those of the fibroblastic or histiocytic type, enter from an unknown source. Two theories accounting for these cells have been devised; first that they arise from the connective tissue and represent a very early form of muscle antecedent; second, that they are derived from the muscle tissue through anaplasia. Those upholding the first theory assert that they can trace the development of the muscle from the connective tissue, through all of the intermediate stages; those supporting the second reverse the condition and see the muscle cells awaking to multiplication and regressing into connective-tissue cells. Both are probably in error, for there would seem to be no more uncertain and misleading method of arriving at the source of cells than the attempt to follow them from one type to the other by picking out and arranging in order those that appear to answer the requirements of “intermediate stages.”
With neither of the theories mentioned above is the writer in sympathy. Both imply the continuous transformation of normal cells to tumor cells, which is incompatible with what is known about tumors. The improbability of muscle tissue originating from other than residual or reserve embryonal muscle cells has already been expressed, and equal doubt exists as to the occurrence of anaplasia. The tumors under consideration should be regarded as complex. They are composed not of muscular tissue alone, but of muscular tissue and some other type of tissue, less highly specialized, that first grows with, then outgrows, and sometimes eventually extinguishes the muscular tissue. It is through this invasion and extinction of the muscle tissue by the "sarcoma" tissue that the former has been supposed to evolve into the latter. The writer does not believe that any other kind of "transformation" or "degeneration" takes place.

But, to return to the problem of nomenclature, by what rule shall the tumors be named? Shall a neoplasm whose seat of occurrence, gross appearance, and general histologic structure classify it among the muscle tumors continue to be so classed if invaded by sarcoma of independent origin? Shall the one tumor whose malignancy results from the invasive and metastatic activities of its own embryonal cells
be a malignant leiomyoma, and another whose invasive and metastatic activities depend upon associated sarcoma be leiomyosarcoma? What shall a tumor in which the two types of tissue occur in both the primary and secondary tumors be called?

Malignancy in unstriated muscle tumors, as in other tumors, is shown by infiltrative invasion, or metastasis, or both. It is, therefore, a clinical manifestation. Naturally, however, the clinician desires to foresee the outcome, and therefore consults the histopathologist. The varying results of the consultation are well expressed in the percentages of malignancy tabulated above. A difference among different pathologists in different institutions by which the incidence of malignancy is made to vary from zero to 10.0 per cent must bespeak radical differences in the evaluation of the microscopic criteria of malignancy. It would seem that those means by which the highest percentage of malignancy is arrived at are most in favor, and this may be only natural since on this basis the highest percentage of operative cures would be obtained.

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. Independent multiple tumors may occur in the same organ or in different organs and must not be compared with metastases.

That the primary tumors are usually multiple in the uterus is common knowledge. One of the gastric tumors reported by Geschickter consisted of multiple nodes in the pyloric region. Pape and Spitznagel observed a case with multiple nodules in the esophagus and stomach. Among the dermatomyomas collected by Ormsby were some with from 20 to 100 separate nodules in the skin. Laboulbene saw four small myomas in the wall of the same stomach. All of these cases were undoubtedly multiple primary tumors, but what of a case referred to the author by Dr. Jonathan Wainwright? Some years after he removed from the uterus a tumor that was described as a "suspicious fibroid," a new tumor appeared in the neck, later another in the thigh, and still later one in the abdominal wall, all of a similar and somewhat peculiar histological structure that suggested origin from the uterine tumor.

Metastasis may take place through the blood or lymph and may occur in the usual distribution—liver, lungs, lymph nodes—but sometimes, as in Wainwright's case, the distribution is perplexing. A tumor of the uterus, sections of which were obtained from Dr. Frank Konzelman of Temple University Hospital, had all its secondaries in or upon the intestines. Dr. Harold M. Dixon performed an autopsy, in the Philadelphia General Hospital, upon a woman whose uterus had been removed for a "malignant tumor" some time previously, whose abdominal viscera were covered with hundreds of peritoneal nodules varying from the size of an egg to that of a pea, all of rapidly multiply-
**Fig. 4. Malignant Uterine Myoma (Removed by Dr. Camille J. Stamm).** × 200

Short cells, polymorphous cells, mitoses regular and irregular, nuclear deformities and abundant giant cells. Death was due to metastasis eight months after hysterectomy.

**Fig. 5. Vaginal Metastasis from the Tumor Illustrated in Fig. 4, Showing the Same General Histologic Structure**
ing unstriped muscular tissue. In still another case, referred to the
author by Dr. E. A. Case of the Graduate School Hospital in Philadel-
phia, there was a single nodule in the vaginal wall supposed to be
secondary to a tumor of the uterus.

Sometimes the metastases are widespread, as in a case in the
Boston City hospital, notes of which were secured by Dr. Leary, in
which the primary tumor was in the uterus, with metastases in lungs,
liver, kidney, pancreas, orbit and rib. Another patient whose uterus,
ovaries and tubes were operatively removed at the Mt. Sinai Hospital
in Philadelphia for fibroids, some of which were "suspicous," later
died in the Jefferson Hospital, where post-mortem examination showed
multiple nodules distributed over the peritoneum, numerous small
nodules in the liver, and a large mediastinal tumor that compressed the
right lung. One of Dr. Tracy Mallory’s patients, in the Massachusetts
General Hospital, had a primary nodular tumor of the duodenum with
invasion of the regional lymph nodes.

Hansemann saw a gastric tumor with metastases in the liver and
pancreas, and Ewing a uterine tumor in which the serous surface of
the organ was covered with miliary nodules. Cohen found in the Phila-
delphia General Hospital records of a case of "leiomyosarcoma" of
the left kidney with metastasis to both lungs, right kidney, suprarenal
glands, ileum, mediastinal and mesenteric lymph nodes, and brain.
If only there were follow-up data upon all of the cases that have been pronounced and published as malignant, the problem of histopathologic prognosis would be simplified, but unfortunately most of the published records conclude with the statement that "the patient made a good recovery"—meaning, of course, from the operation.

What are the histologic criteria by which the benignancy or malignancy of myomatous tumors is estimated? This matter has been carefully considered by Newton Evans of the Mayo Clinic, who drew his conclusions from the study of 72 tumors. They accord with most of the previous writings upon the subject and are as follows: increase in the size of the tumor cells; shorter, plumper cells with more oval nuclei; inequality and irregularity in the size and shape of the cells; lack of differentiation in the cells; unequal and especially deep staining of the nuclei; presence of unusual cells (protoplasmic plaques) with hyperchromatic single and multiple nuclei (giant cells); presence of mitotic figures typical and atypical, especially pluripolar mitoses; decrease or absence of stroma fibers between the cells; thinness or absence of blood vessel walls.

How reliable are these changes? All may be absent and the tumors appear exactly like simple benign fibroids, yet the tumors be metastatic, as in the Group I of Costa. Melnik's primary tumor of the stomach seemed to be a simple benign leiomyoma, yet there was a supposed metastasis of identical structure in the liver. Vogt thinks that though these characters are important, they may mean no more than temporary acceleration of growth and that they may later subside and regress.

Much time has been spent in going over the sections of supposed malignant myomas in the writer's private collection, with the view of testing the criteria of malignancy just given. Most of them were present and well marked in all of the fatal cases. But unfortunately many of them, including giant cells, were present in many of those 34 cases in which neither the reappearance of the tumor nor the death of the patient is known to have taken place. At present I am constrained to conclude with Döring that the occurrence of metastasis is the only proof of malignancy.

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