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# Mixed Mesodermal Tumors of the Uterus

JOSE F. AFONSO, MD, *Hayward, California*

*Two of five women with mixed mesodermal tumor of the uterus are well more than ten years after therapy. A third was well when last seen two years after therapy and died at age 84 but autopsy was not done.*

*Review of the literature and the reported experience indicates that this diagnosis should be suspected more often. Since histologic features may vary from one place to another within the lesion, accurate assessment requires examination of adequate specimens of the tumor. The mere presence of heterologous elements in an endometrial carcinoma changes the five-year survival rate from 85 percent to less than 35 percent. While total abdominal hysterectomy with bilateral salpingo-oophorectomy is mandatory, radiation therapy should be added more often than in the past, as it has been clearly shown that many of these tumors are radiosensitive.*

MIXED MESODERMAL TUMORS of the uterus are considered to be among the most malignant of neoplasms. Although they are relatively rare, accounting for only 0.2 percent or fewer of all gynecologic hospital admissions,[1] they derive clinical importance from an association with previous radiation therapy, and from the success of treatment in a number of cases.

The classification of these neoplasms has been controversial ever since Kehrer[2] proposed the term *mixed mesodermal tumor* in 1906. By 1935, McFarland[3] had collected 119 names representing attempts to designate the gross or microscopic features in individual cases. The basic neoplastic element is mesenchymal sarcoma, often called "undifferentiated cellular sarcoma," "endometrial sarcoma," or "fibromyxosarcoma." Other histologic components appear as discrete islands surrounded by the sarcomatous background. In various tumors, and in areas of the same tumor, there may be rhabdomyosarcoma, chondrosarcoma, leiomyosarcoma, fibrosarcoma or liposarcoma, singly or in diverse combinations. Carcinomatous elements are also frequent; the most common is endometrial carcinoma, but epidermoid, papillary or mucinous adenocarcinoma is often present.

The degree of differentiation and the relative proportions of all elements vary widely. One histologic component may so predominate that if an insufficient sample is obtained, the tumor may be misdiagnosed according to that single element.

Zenker,[4] in 1864, classified as "pure" those

From the Department of Obstetrics and Gynecology, Kaiser-Permanente Medical Center, Hayward.

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Reprint requests to: J. F. Afonso, MD, Kaiser-Permanente Medical Center, 27400 Hesperian Boulevard, Hayward, CA 94545.

TABLE 1.—*Comparative Frequency of Mixed Mesodermal and Other Malignant Tumors of the Uterus*

| Report by | Mixed Mesodermal | Carcinoma | |
|---|---|---|---|
| | | Cervix | Endometrium |
| Symmonds and Dockerty, 1959[9] | 1 | 345 | 143 |
| Krupp et al, 1961[10] | 1 | 120 | 14 |
| Edwards et al, 1963[11] | 7 | ... | 475 |
| Falkinburg et al, 1964[12] | 1 | ... | 30 |
| Mortel et al, 1970[13] | 9 | ... | 150 |

TABLE 2.—*Reported Cases of Mixed Mesodermal Tumors of the Uterus*

| Report by | Number of Cases | Year |
|---|---|---|
| Speert and Peightal[14] | 4 | 1949 |
| McElin and Davis[15] | 2 | 1952 |
| Schiffer, Mackles, and Wolfe[16] | 5 | 1955 |
| Taylor[17] | 26 | 1958 |
| Ober and Tovell[18] | 12 | 1959 |
| Ricciutti, Noble, and Kiefer[19] | 1 | 1961 |
| Heinrichs, Climie, and Cook[20] | 1 | 1962 |
| Edwards et al (review)[11] | 295 | 1963 |
| Falkinburg et al[12] | 6 | 1964 |
| Rachmaninoff and Climie[21] | 30 | 1966 |
| Chaves[22] | 3 | 1966 |
| Norris, Roth, and Taylor[23] | 31 | 1966 |
| Mendel, Lucas, and Panopio[24] | 15 | 1967 |
| Persaud and Knight[25] | 4 | 1968 |
| Gudgeon[26] | 1 | 1968 |
| Ruffolo, Metts, and Sanders[27] | 9 | 1969 |
| Masterson and Kremper[28] | 25 | 1969 |
| Edwards[29] | 85 | 1969 |
| Chuang, Van Velden, and Graham[1] | 20 | 1970 |
| Glover[30] | 1 | 1970 |
| Mortel et al[13] | 9 | 1970 |
| Reddy, Bharma, and Sankaran[31] | 1 | 1970 |
| Schaepman-Van Guens[32] | 29 | 1970 |
| Giarratano and Slate[33] | 4 | 1971 |
| Total | 499 | |

mesenchymal sarcomas that are composed of a single cell type; as "mixed," those comprising more than one cell type. He classified as "homologous" those made up of tissue elements indigenous to the uterus, and as "heterologous" those containing tissue elements normally foreign to the uterus. On this basis, Ober,[5] in 1958, proposed an elaborate but clear classification of mesenchymal sarcomas, useful where an adequate specimen is properly studied. According to that classification, any uterine cancer that contains stromal sarcoma plus one or more heterologous elements, or that contains two or more heterologous elements, should be coded "mixed mesodermal tumor." The carcinomatous components of mixed mesodermal tumors, unlike the sarcomatous elements, are limited by the potentialities of the müllerian tract.

Mixed mesodermal tumors characteristically originate in the stroma of the genital tract, immediately beneath the lining epithelium, which is frequently intact. They are often of multicentric origin, and seem never to arise deep within the uterine wall. Of the two main hypotheses that have been advanced for their histogenesis, the cell rest theory suggested by Cohnheim[6] in 1875 is incompatible with modern concepts of carcinogenesis. In 1892, Pfannenstiel[7] proposed that they arise by metaplasia from uterine mesodermal tissue. It is now generally believed that they arise in situ from endometrial[8] and endocervical stroma. This, the most primitive uterine tissue, has in common with other mesenchymal cells the ca-

TABLE 3.—*Patient Characteristics and Presenting Manifestations*

| Patient | Race | Age | Gravida/ Para/ Abortions | Marital Status | Interval Since Last Menstrual Period | Past History and Presenting Manifestations |
|---|---|---|---|---|---|---|
| 1 | White | 53 | 3/2/1 | Married | 3 Weeks | Normal menstrual history. Watery vaginal discharge 3 months |
| 2 | White | 41 | 0 | Single | 5 Days | Normal menstrual history. Persistent intermenstrual vaginal spotting 5 months. 5 days after onset of last menstrual period, low abdominal cramps; passed tissue 12.5 × 7.5 × 3.5 cm per vagina; diagnosed leiomyosarcoma |
| 3 | White | 82 | 5/5/0 | Widowed | 30 Years | Intermittent slight vaginal bleeding 8 months |
| 4 | White | 61 | 0 | Single | 13 Years | During anticoagulant therapy for thrombophlebitis 6 months ago, vaginal spotting; persisted. Heavy vaginal bleeding 4 days ago, 2 to 3 soaked towels daily. Lost 20 pounds preceding year. Treated for diabetes mellitus 7 years; for arteriosclerotic cardiovascular disease with congestive heart failure 6 months. Right oophorectomy, tubal ligation 30 years ago |
| 5 | Black | 64 | 4/3/1 | Married | 15 Years | Gush of bright red blood per vagina 3 months ago; then persistent vaginal bleeding (2 to 3 pads daily) and foul vaginal discharge. Lost 45 pounds preceding year |

pacity to differentiate into many mesenchymal derivatives (striated muscle, cartilage, fat) as well as into epithelial structures characteristic of the müllerian tract. This is understandable when we recall that, except for its nerves, the entire uterus is of mesodermal origin.

The rarity of mixed mesodermal tumors relative to the occurrence of other malignant tumors of the uterus as reported by several observers[9-13] is apparent from Table 1. Only 499 cases appear to have been reported hitherto[11-30,31-33] (Table 2). Added to those are the five cases whose salient features are summarized in Tables 3, 4 and 5 in lieu of individual case reports.

Some investigators have suggested that race, parity, or sexual activity may correlate with the incidence of these tumors. It has been proposed that they occur more often in blacks than in whites;[23,36] and the reverse has been observed.[1] The same contradictions can be found with regard to parity and sexual activity.[1,9,15]

### Site of Origin Related to Menstrual Status

The most common site of origin of mixed mesodermal tumors of the uterus is the corpus, where they are found almost exclusively in menopausal and postmenopausal women. This diagnosis is occasionally made during adolescence but seldom during the reproductive years. In women of this age range, mixed mesodermal uterine tumors usually start in the cervix. During infancy and childhood, the juvenile member of this family of tumors, botryoid sarcoma, usually begins in the vagina.

Patient 1 of the present report was 53 years of age and still menstruating; the tumor had its origin in the cervical stroma. In Patients 2 to 5, the tumor began in the endometrial stroma.

Mixed mesodermal tumors, as well as carcinosarcomas, have been reported as primary ovarian tumors; but this is extremely rare, and such neoplasms are believed to originate in areas of endometriosis.[34,35]

### Radiation Therapy: Possible Etiologic Factor

The majority of the uterine neoplasms that arise after radiation therapy are mixed mesodermal tumors or carcinosarcomas. Although a causative relation cannot be established because the cases have been few, follow-up data are incomplete and many variables are involved, an association between the appearance of mixed mesodermal tumors and previous radiation to the pelvis has been reported by many observers. The carcinogenic activity of radiation appears to be greater with small than with large doses; neoplasia therefore more often follows such treatment for benign than for malignant lesions. Thirty-six (10 percent) of the 360 patients listed in Table 6 had received radiotherapy for benign lesions; 14 (3.8 percent) for other malignant neoplasms. The intervals between radiotherapy and the diagnosis of mixed mesodermal tumor ranged from four years to 36 years, except that one tumor developed a year after radiation for benign disease[24] and another arose while the patient was receiving chemotherapy after radiation for ovarian cystadenocarcinoma.[26] None of the five patients of the present series had received radiotherapy in the past.

Since an association does exist and the interval between exposure and the appearance of the tumor may be long, patients who have received radiation therapy to the pelvic region should be observed periodically longer than 20 years with the possibility of postirradiation cancer in view. In treating younger women for cancer, whenever the cure rates of radiotherapy and surgical excision are equivalent, the latter should be chosen. It is heartbreaking to find a mixed mesodermal tumor or carcinosarcoma of the uterus ten or more years after the apparent cure of another gynecologic cancer.

### Signs and Symptoms

The manifestations of mixed mesodermal tumor are nonspecific. Abnormal vaginal bleeding is the presenting complaint of 80 to 90 percent of patients with this disease. Crampy lower abdominal pain, foul watery or purulent vaginal discharge, passage of fragments of necrotic tissue per vagina, and weight loss are frequent. Three of the patients in the present series had postmenopausal bleeding; one had only watery vaginal discharge, and another had intermenstrual bleeding with cramps in the lower part of the abdomen.

Pelvic examination often leads to prompt consideration of this diagnosis, as in 30 to 50 percent of the cases a polypoid tumor protrudes from the cervical os or within the cervical canal or, occasionally, through the vaginal introitus. Mixed mesodermal tumors are frequently bulky, friable, soft and fleshy, fungating and occasionally necrotic, reddish purple or whitish gray. In many instances, however, the only abnormal finding is uterine enlargement, with or without irregularity of contour; for early lesions, the findings are usually normal.

TABLE 4.—*Pertinent Findings on Initial Examination**

| *Patient* | *Physical Examination* | *Pelvic Examination* | *Papanicolaou Smear* | *Biopsy* | *Roentgenography†* |
|---|---|---|---|---|---|
| 1 .... | Normal | Pedunculated whitish-gray mass protruded from cervical os | .... | ..... | ..... |
| 2 .... | Irregular, nontender, globular, firm pelvic mass to 7 cm above symphysis pubis | Reddish-purple polypoid mass protruded from cervical os; os dilated to 1.5 cm. Uterine fundus anteverted, freely movable, globular, 16-weeks gestation size | Class I | Chronic cervicitis | Routine views normal |
| 3 .... | Well-nourished, healthy. Firm, regular, movable, tender mass, lower abdomen to 11 cm above symphysis pubis | Necrotic, cyanotic, 4 × 3 × 3-cm mass protruded through external cervical os; os 2 cm dilated. Cervix bled easily on contact. On bimanual examination, cervix firm, dilated 2 cm around firm mass. Uterine fundus irregular, firm, mobile, 16-weeks gestation size | Class I | *Cervix:* normal. *Protruding mass:* endocervical polyp. *D&C:* 350-gm soft, grayish, multinodular tissue: mixed mesodermal sarcoma | Routine views, skull films, barium enema normal. Excretory urography showed large soft-tissue pelvic mass |
| 4 .... | Obese; BP 200/100; mild cardiomegaly; optic fundi Keith-Wagner grade ii. | 6 × 3-cm exophytic, pedunculated, friable, hemorrhagic mass arising from middle ⅓ of posterior vaginal wall protruded through vaginal introitus. Cervix slightly dilated; polypoid, friable tissue through external os. Uterine fundus anteverted, 8-weeks gestation size. Adnexae poorly outlined. No palpable masses | Class II | *Mass at vaginal introitus:* necrotic hemorrhagic tissue. *Vaginal lesion:* pleomorphic neoplasm, adenoid, sarcomatoid, anaplastic elements. Giant and multinucleated cells; cells suggesting myogenic differentiation. *Diagnosis:* mixed mesodermal tumor | Plain film of abdomen, barium enema, excretory urogram, lateral view of lumbosacral spine normal. *Chest:* 2 nodules, 1 × 2 cm, in each lung field |
| 5 .... | Confused, lethargic, obese; BP 160/90; pulse 90; cataract left eye. Firm, fixed, nontender mass, lower abdomen to 2 cm above umbilicus | Perineum covered with foul-smelling, feces-like vaginal discharge. Cervix not identifiable. Tongues of necrotic tissue filled vaginal apex, protruded into vaginal canal. Pelvic cavity filled wall-to-wall with hard, fixed mass (frozen pelvis) to umbilicus | .... | ..... | Chest: normal |

*Findings in blood and urine were normal or nonspecific for this disease. In Patient 4, electrocardiogram showed left axis deviation, digitalis effect. Patient 5's urine was loaded with white and red blood cells and bacteria; hematocrit 31 percent; leukocyte count 21,200; blood urea nitrogen 148 mg per 100 ml; other abnormalities of blood chemistry typical of terminal disease.

†Chest film, excretory urography, and lateral view of lumbosacral spine are here designated "routine."

In other cases, the entire pelvic contents appear to be replaced by tumor. The ascites, cachexia, and masses throughout the abdomen which are seen in advanced disease suggest ovarian cancer. Thus, in a large proportion of patients, the results of the physical examination are not diagnostic of mixed mesodermal tumor.

## Pathologic Findings

*Gross Appearance*

A polypoid growth usually fills the endometrial cavity. The tumor mass may be single or multiple; its consistency may vary from fairly firm to soft and fleshy. The base of the tumor may be broad or narrow, but demarcation from the underlying myometrium is usually distinct. As in Patient 3 of this report, the tumor may appear as globular, firm elevations of the endometrial surface measuring less than a centimeter in diameter.

Although there is no causal relation between uterine leiomyomata and mixed mesodermal tumors, they often coexist. The finding of a soft polypoid mass within a uterine cavity containing leiomyomata may lead one to assume erroneously that a submucous fibroid tumor has undergone degeneration or malignant change.

The cut surface of a mixed mesodermal tumor is usually soft and moist and grayish white, pinkish or purple; there are usually hemorrhage and necrosis; occasionally there are areas of gelatinous softening or cyst formation.

*Microscopic Appearance*

The background of the varied histologic structure that is presented by mixed mesodermal tumors is endometrial sarcoma, characterized by poorly differentiated cells with sparse cytoplasm, crowded nuclei, and indefinite borders. Within this basic neoplasm, tissue or tissues are found which have no benign counterpart in the uterus (heterologous). Of these, striated muscle and cartilage are encountered most commonly.

In the opinion of a minority of observers,[41] the *sine qua non* for the diagnosis of mixed mesodermal tumor of the uterus is the presence of embryonal myoblasts. Some investigators insist on the presence of typical longitudinal and transverse striations, permitting identification of the cells as being of striated muscle origin. The majority,[1,28,39,44] however, accept as sufficient proof the presence of numerous pleomorphic cells with abundant eosinophilic cytoplasm having a "strap" or "tadpole" shape. The tissue culture studies of Murray and Pogogeff[42,43] showed that spindle cells with intensely eosinophilic and perhaps granular cytoplasm are embryonic rhabdomyoblasts in a stage of development preceding the development of cross striations.

If one accepts Ober's classification,[5] the presence of carcinomatous elements, whether squamous or adenoid, will place the tumor in the category, carcinosarcoma with heterologous elements. Most other investigators[1,13,28,39] define carcinosarcomas as those tumors which are composed only of sarcomatous and carcinomatous elements; they reserve the term *mixed mesodermal tumor* for those which contain, in addition, heterologous elements.

Some observers[10,21,44] consider such a distinction to be valueless because the clinical features, treatment, prognosis and gross pathologic features of these two types of cancer show no significant differences. Others[23,32] have found sufficient behavioral differences to continue the separate classifications on the basis of their definitive microscopic features. Schaepman-Van Geuns[32] reported a 14 percent better survival rate associated with carcinosarcomas than with mixed mesodermal tumors.

## Mode of Spread

Mixed mesodermal tumors invade surrounding tissues by continuity, through lymphatic channels, and through the blood stream, as indicated by study of the tumor and surrounding tissues, the appearance of metastasis, and the sites of recurrence. Some observers[1,13,28] have found that the soft tissues and lymph nodes of the pelvis are involved in most patients, and that local recurrence is frequent. Others[10,21] have emphasized that distant metastasis is the rule rather than the exception, and that hematogenous spread is more frequent than lymphatic. The most common sites of metastasis are the lungs, pleura, vagina, omentum, mesentery, ovaries and extrapelvic lymph nodes. One or more tissues seen in the primary tumor may occur in the metastatic site, so that either or both of the sarcomatous and carcinomatous elements may be clearly distinguished.

## Diagnosis

Because the majority of patients complain of abnormal uterine bleeding, dilatation and curettage is a frequent diagnostic procedure. In 25 to 50 percent of the cases, the diagnosis of mixed

TABLE 5.—*Treatment, Gross and Microscopic Findings, and Outcome*

| *Patient* | *Treatment* | *Gross Appearance of Tumor* | *Microscopic Findings* | *Outcome* |
|---|---|---|---|---|
| 1 ..... | (a) Tumor exised; scalpel conization of cervix; dilatation and curettage | Smooth outer cover. Cut surface coarsely lobulated, uniformly gray; brain-like consistency | Round cell sarcoma, areas of myxosarcoma and adenocarcinoma; in other areas stromal sarcoma, chondrosarcoma, adenocarcinoma merged (Figure 1). Endometrial cuttings normal. *Conization specimen:* cervical stroma infiltrated by adenocarcinoma | ..... |
| | (b) Radium (5 Carmel applications, each with 10 mg of radium, 2 vaginal ovoids, each with 25 mg of radium = 5,000 r to Point A). Six weeks later, total abdominal hysterectomy with bilateral salpingo-oophorectomy. Postoperative cobalt = 4,000 rads to pelvic midplane | At hysterectomy, slight uterine enlargement only visible abnormality | Necrotic endometrium, myometrial infiltration by adenocarcinoma to serosa; extensive perivascular and lymphatic invasion. Cervix infiltrated by glandular carcinoma; tumor within lymphatic vessels | Patient well, no recurrence, 11 years and 6 months after hysterectomy |
| 2 ..... | Total abdominal hystrectomy, bilateral salpingo-oophorectomy | Uterine fundus 16-18 weeks' gestational size; leiomyoma on posterior surface. Right ovary 6 × 3.5 × 4 cm; left normal. In opened uterus, fungating, polypoid, necrotic, racemose mass arising from left side. Uterine wall contained many leiomyomata | *Uterine and ovarian tissue:* anaplastic sarcoma cells, large undifferentiated cells suggestive of embryonic muscle cells, nests of squamous cell carcinoma, myxosarcoma. Neoplasm apparently originated just beneath endometrium; minimal myometrial invasion | Patient well, 10 years after hysterectomy |
| 3 ..... | Total abdominal hysterectomy, bilateral salpingo-oophorectomy | Uterus 12 weeks' gestational size. Many 3 × 2 cm subserous leiomyomata. Endometrial surface: many globular elevations 0.5 cm greatest diameter. Tubes, ovaries normal | *Endometrial nodules:* pleomorphic spindle-shaped cells, adenocarcinoma, some rhabdomyoblasts, typical tadpole cell (Figure 2). No myometrial invasion | No recurrence 2 years later. Died 1 month later (age 84); no autopsy |
| 4 ..... | Desmethylcolchicine, 0.5 mg/kg i.v., 6 days; 2 days interruption, repeated 3 days. Toxic, ineffective. Transvaginal x-ray, 2,400 r in air over 9 days: 3 weeks later, vaginal lesion had melted away, but many minute, easily bleeding polypoid lesions in posterior vaginal wall. Local radium to vaginal mucosa, 4,155 r: one month later, vagina scarred, stenosed, no visible or palpable tumor; chest lesions larger. 5-Fluorouracil: slight, transient decrease in pulmonary nodule size, no apparent effect on primary tumor; toxic (WBC 1,400/mm$^3$) | *Autopsy:* 1 × 4 cm pearly white nodules throughout both lungs and peritoneal cavity; left adrenal gland replaced by tumor; uterus replaced by 20 × 30 cm, soft, necrotic mass; tubes and ovaries involved | *Uterine tumor:* pleomorphic sarcoma, adenocarcinoma, embryonic rhabdomyoblasts. *Pulmonary metastatic lesions:* exclusively stromal sarcoma | Died 7 months after admission (pelvic mass above umbilicus; ascites; dyspnea) |
| 5 ..... ..... | | *Autopsy:* pelvic tumor 2 cm above umbilicus replaced uterine fundus. Fallopian tubes normal; ovaries atrophic. Uterine fundus: many leiomyomata; cavity filled with polypoid, soft tumors arising near endocervix, extending into vaginal canal. Bilateral ureteral obstruction; no rectal involvement | *Polypoid tumors:* undifferentiated stromal sarcoma with many giant cells, typical tadpole cells (rhabdomyoblasts). *Other areas:* adenocarcinoma in thick tongues of tissue surrounded by fibrosarcoma. | Died of anemia 3 days after admission |

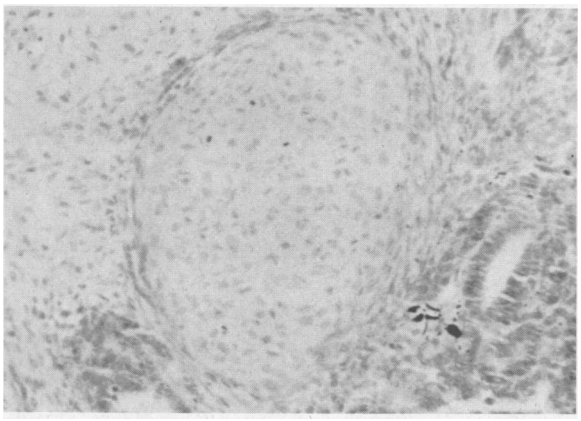

**Figure 1.—Merging areas of stromal sarcoma, adenocarcinoma, and chondrosarcoma.**

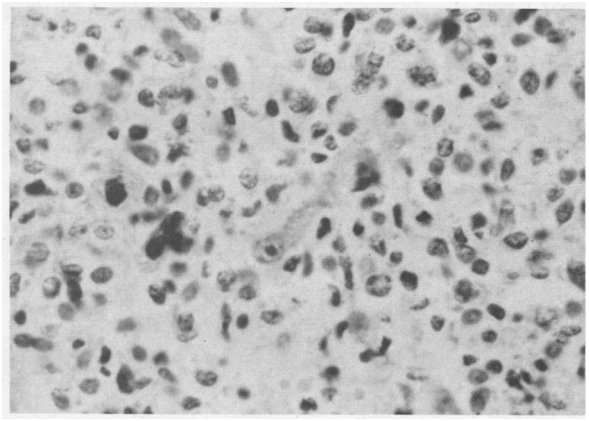

**Figure 2.—Stromal sarcoma with typical "tadpole" cells representing rhabdomyoblasts.**

mesodermal tumor is missed by this method,[1,28] but the presence of malignant neoplasia is established. Endometrial sarcoma or adenocarcinoma is the most frequent initial diagnosis. Biopsy of the mass that protrudes through the cervical os frequently yields the necessary information, but in many cases only sarcomatous or carcinomatous elements, or what appears to be pure leiomyosarcoma is found, and occasionally there is so much necrosis that no structure can be identified with certainty. In a large number of patients the diagnosis of carcinosarcoma is made, and is changed only after extensive recutting of the specimens with painstaking review of new slides, where heterologous cells are finally found. Often the correct diagnosis is made only after hysterectomy or at autopsy.

## Treatment

Review of reported cases shows that a multitude of treatments have been used, all with poor results. Often no treatment was possible or only palliation could be used. The preferred approach is surgical; the minimal procedure contemplated should be total hysterectomy with bilateral salpingo-oophorectomy. If the tumor has originated in or extended to the cervix, radical hysterectomy with pelvic lymphadenectomy is indicated. A few investigators[10,23,36,38] have advised radical hysterectomy with pelvic lymphadenectomy as the initial surgical procedure, irrespective of cervical involvement. The value of regional lymph node removal is questioned by those who believe that these tumors tend to metastasize through the blood rather than the lymph. Two of the patients in the series here reported are living and well more than ten years after total abdominal hysterectomy with bilateral salpingo-oophorectomy; one also received radiation therapy—preoperatively with radium, and postoperatively with cobalt. Patient 3 was treated by total abdominal hysterectomy with bilateral salpingo-oophorectomy alone, and two years later appeared to be free of disease. She died a month after having been seen, at the age of 84.

Some observers[27,32] have expressed serious reservation about the value of radiation therapy, preoperatively or postoperatively, for this disease. Others[10,21,23,25,36,38,45] appear convinced that mixed mesodermal tumors are radioresistant, and that preoperative radiation merely delays treatment; still others,[13,29] that radiation should be added to the surgical procedure either preoperatively[13,29] in the form of radium therapy, or postoperatively as external radiation.[9,12,18] Chuang and colleagues[1] found that neither preoperative nor postoperative radiation affected five-year survival rates, whereas Edwards[29] reported a significant improvement with preoperative radium therapy, and Mortel and coworkers[13] pointed out that, of 26 previously reported patients who had survived five years, 18 had received some form of radiation therapy.

There is no question that some mixed mesodermal tumors are sensitive to radiation.[13,20,29] Kempers, in discussing the paper by Masterson and Kremper,[28] mentioned one patient who had received only palliative irradiation, then lived six and a half years with clinical regression of the tumor. One of the two five-year survivors reported by Edwards and colleagues[11] was treated for recurrence of tumor in the parametrium after subtotal hysterectomy, by local perfusion with gold, irradiation with radium, external radiation and nitrogen mustard. The response in the vaginal

TABLE 6.—*Role of Radiation Therapy in the Development of Mixed Mesodermal Tumors*

| Report by | Number of Patients | Previous Radiation: Benign Lesion | Previous Radiation: Malignant Disease | Interval (years) |
|---|---|---|---|---|
| Chuang et al[1] | 20 | .. | 3 | 7-29 |
| Krupp et al[10] | 51 | .. | 2 | 11-13 |
| Edwards et al[11] | 7 | 1 | 2 | 6-10 |
| Mortel et al[13] | 9 | 1 | .. | 28 |
| Speert and Peightal[14] | 4 | 3 | .. | 9-14 |
| McElin and Davis[15] | 2 | 2 | .. | 11-20 |
| Schiffer et al[16] | 5 | 1 | .. | 6 |
| Taylor[17] | 40 | 3 | .. | ? |
| Ober and Tovell[18] | 12 | 1 | .. | ? |
| Heinrichs et al[20] | 1 | .. | .. | .... |
| Rachmaninoff and Climie[21] | 30 | .. | .. | .... |
| Norris et al[23] | 31 | 6 | 3 | 7-26 |
| Mendel et al[24] | 15 | 1 | .. | 1 |
| Gudgeon[26] | 1 | .. | 1 | 1.5 |
| Ruffolo et al[27] | 9 | 1 | .. | ? |
| Masterson and Kremper[28] | 25 | 3 | 2 | 4-23 |
| Reddy et al[31] | 1 | .. | .. | .... |
| Schaepman-Van Guens[32] | 29 | 3 | 1 | 7-31 |
| Sternberg et al[36] | 21 | .. | .. | .... |
| Aaro et al[37] | 26 | 6 | .. | 4-36 |
| Hill and Miller[38] | 4 | 2 | .. | 10-11 |
| Marcella and Cromer[39] | 11 | 1 | .. | 6 |
| Rubin[40] | 1 | 1 | .. | ? |
| Present series | 5 | .. | .. | .... |
| Totals | 360 | 36 | 14 | |

lesion of Patient 4 of the present series also indicates radiosensitivity.

Radiation alone is used for palliation, as are various forms of chemotherapy. Nitrogen mustard and thioTEPA have been found ineffective.[10,11,36,39] In one reported patient,[26] the tumor developed during chlorambucil therapy; in another, 5-fluorouracil had no apparent effect.[11] Worthwhile palliation has been reported with cyclophosphamide,[28,32] but Glover,[30] using it in a single case, saw no benefit from this drug. In our Patient 4, neither desmethylcolchicine nor 5-fluorouracil afforded significant palliation.

## Prognosis

Although extremely poor, the prognosis is not entirely hopeless. Determination of accurate five-year survival rates from reported cases is impeded by the short time elapsing between treatment and report in many instances, by loss of patients to follow-up, and by the inclusion of carcinosarcomas in some series. Excluding those series in which no patient survived as long as five years, Table 7 shows the numbers and percentages of five-year survivors in the 15 remaining reports, and the types of treatment given. The five-year survival rates ranged from 9 percent to 40 percent for an average of 21.3 percent (57 of 267 patients). When series in which all patients died within five years* are included, only 57 of 362 patients (15.7 percent) had this outcome. No conclusion can be drawn with regard to the effectiveness of the type of treatment employed, as it is not clear how many patients in each category died, were lost to follow-up, or had received therapy less than five years previously.

Search for factors that would serve as reliable prognostic indices has elicited some contradictory findings, as well as observations confirmed by most observers. Chuang and coworkers[1] saw no correlation between the number of mitoses per high-power field and survival rates, and noted that a history of irradiation for cancer suggested an extremely poor prognosis. Edwards and colleagues[11] saw no relation between duration of symptoms or early diagnosis and outcome. Survival rates appear to be higher in younger than in older women.[21,32] The influence of specific heterologous elements on survival has been evaluated with contradictory results. The presence of cartilage has been considered a bad prognostic sign by some,[25,47] a good prognostic sign by others,[23] and of no significance by most.[1,28,32] The prognosis is not unfavorably influenced by the presence of a rhabdomyosarcomatous component.[1,21,32]

The two most important prognostic factors are the degree of myometrial infiltration and the extent to which tumor involves other structures. It is interesting, however, to note that all of the four long-term survivors reported by Masterson and Kremper[28] had microscopic invasion of the blood vessels, and one had extension to the uterine serosa.

Our two surviving patients (Patients 1 and 2) were relatively young—41 and 53 years of age; one had extension of the tumor to the right ovary, the other to the uterine serosa with extensive perivascular and lymphatic invasion. One had had symptoms for three, the other for five months before first examination. Cartilage was present in only one. In Patients 4 and 5, who died, the disease was extensive and beyond hope of cure when they were first seen.

The majority of recurrences take place within the first year, but some have appeared three to five years after treatment of the first tumor. The majority of reported patients who died of the dis-

*References 10,16,19,20,26,27,30,33,36,40

TABLE 7.—*Treatment and Five-year Survivals in Series of Patients Followed for at Least Five Years*

| Report by | Number of Patients | Radical Hysterectomy | TAH* | TAH, BSO† | Preoperative Radiation, TAH, BSO | TAH, BSO, Postoperative Radiation | Preoperative & Postoperative Radiation TAH, BSO | Subtotal Hysterectomy, Radiation | Radiation Only | Five-year Survivals | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | No. | Percent |
| Chuang et al[1] | 20 | .. | .. | 2 | .. | .. | .. | .. | .. | 2 | 12 |
| Symonds and Dockerty[9] | 19 | .. | .. | 2 | .. | 2 | .. | .. | .. | 4 | 21 |
| Edwards et al[11] | 7 | .. | .. | .. | 1 | .. | .. | 1‡ | .. | 2 | 28 |
| Falkinburg et al[12] | 6 | .. | .. | 1 | .. | .. | .. | .. | .. | 1 | 16 |
| Mortel et al[13] | 7 | .. | .. | .. | .. | .. | .. | .. | 1 | 1 | 14 |
| Taylor[17] | 26 | 1 | .. | 1 | .. | .. | .. | 1§ | .. | 3 | 11 |
| Rachmaninoff and Climie[21] | 28 | .. | 2 | .. | .. | 3 | .. | .. | 1 | 6 | 21 |
| Norris et al[23] | 31 | .. | 1 | 1 | 4 | .. | .. | .. | .. | 6 | 19 |
| Masterson and Kremper[25] | 25 | .. | .. | 2 | 1 | 1 | .. | .. | .. | 4 | 15 |
| Edwards[29] | 34 | .. | .. | 2 | 9 | .. | .. | .. | .. | 11 | 32 |
| Schaepman-Van Guens[32] | 33 | .. | 1 | 9 | .. | .. | .. | .. | .. | 10 | 33 |
| Marcella and Cromer[39] | 11 | 1 | .. | .. | .. | .. | .. | .. | .. | 1 | 9 |
| Vellios et al[46] | 9 | .. | .. | .. | 3 | .. | .. | .. | .. | 3 | 33 |
| Carter and McDonald[45] | 6 | .. | .. | .. | .. | 1 | .. | .. | .. | 1 | 16 |
| Present series | 5 | .. | .. | 1 | .. | .. | 1 | .. | .. | 2 | 40 |
| Totals | 267 | 2 | 4 | 21 | 18 | 7 | 1 | 2 | 2 | 57 | 21.3 |

*Total abdominal hysterectomy.
†Bilateral salpingo-oophorectomy.
‡Patient also received nitrogen mustard and perfusion with gold, in addition to radium and x-ray.
§Local removal followed by x-ray and radium therapy.

ease had lived eight to twelve months after diagnosis.

It is clear that the diagnosis of mixed mesodermal tumor of the uterus should be suspected more often, and that adequate biopsy specimens should be taken from uterine tumors which may be of this type to allow for accurate diagnosis. In view of the evidence that many mixed mesodermal tumors are radiosensitive, radiation therapy should be used more frequently in treating them.

## REFERENCES


1. Chuang JT, Van Velden DJJ, Graham JB: Carcinosarcoma and mixed mesodermal tumor of the uterine corpus—Review of 49 cases. Obstet Gynecol 35:769-780, May 1970

2. Kehrer E: Uber heterologe mesodermale Neubildungen der weiblichen Genitalien. Monatschr f Geburtsh u Gynäk 23:646-681, 1906

3. McFarland J: Dysontogenic and mixed tumors of the urogenital region. Surg Gynec Obstet 61:42-57, Jul 1935

4. Zenker FA: Uber die Veränderungen der willkürlichen Muskeln im Typhus abdominalis: Nebst einem Excurs über die pathologische Neubildung quergestreiften Muskelgewebes. Leipzig, FCS Vogel, 1864, pp 84-86

5. Ober WB: Uterine sarcomas: histogenesis and taxonomy. Ann New York Acad Sci 75:568-585, Jan 9 1959

6. von Conheim J: Congenitales quergestreifter Muskelsarcom der Nieren. Arch path Anat Physiol 65:64-69, 1875

7. Pfannenstiel J: Das traubige Sarcon der Cervix uteri. Virchows Arch path Anat 127:305-337, 1892

8. Papanicolaou GN, Maddi FV: Observations on the behavior of human endometrial cells in tissue culture. Am J Obstet Gynecol 76:601-618, Sep 1958

9. Symmonds RE, Dockerty MB: Sarcoma and sarcoma-like proliferations of the endometrial stroma. I. A clinicopathologic study of 19 mesodermal mixed tumors. Surg Gynec Obstet 100: 232-242, Feb 1955

10. Krupp PJ Jr, Sternberg WH, Clark WH, et al: Malignant mixed Müllerian neoplasms (mixed mesodermal tumors). Am J Obstet Gynecol 81:959-969, May 1961

11. Edwards DL, Sterling LN, Keller RH, et al: Mixed heterologous mesenchymal sarcomas (mixed mesodermal sarcomas) of the uterus. Addition of 7 cases. Am J Obstet Gynecol 85:1002-1011, Apr 15, 1963

12. Falkinburg LW, Hoey WO, Savran J, et al: Mesodermal mixed tumor of the corpus uteri—Review and report of six cases, one of which has survived fifteen years. Am J Obstet Gynecol 90: 450-459, Oct 15, 1964

13. Mortel R, Nedwich A, Lewis GC Jr, et al: Malignant mixed müllerian tumors of the uterine corpus. Obstet Gynecol 35:468-480, Mar 1970

14. Speert H, Peightal TC: Malignant tumors of the uterine fundus subsequent to irradiation for benign pelvic conditions. Am J Obstet Gynecol 57:261-273, Feb 1949

15. McElin TW, Davis H Jr: Mesodermal mixed tumor of the corpus uteri. Am J Obstet Gynecol 63:605-612, Mar 1952

16. Schiffer MA, Mackles A, Wolfe SA: Reappraisal of the diagnosis in uterine sarcoma—Review of forty-nine cases. Am J Obstet Gynecol 70:521-539, Sep 1955

17. Taylor CW: Mesodermal mixed tumours of the female genital tract. J Obstet Gynecol Brit Emp 65:177-188, Apr 1958

18. Ober WB, Tovell HMM: Mesenchymal sarcomas of the uterus. Am J Obstet Gynecol 77:246-268, Feb 1959

19. Ricciutti V, Noble AJ, Kiefer L: Malignant mixed mesodermal tumor of the uterus—Report of a case. Obstet Gynecol 18:757-762, Dec 1961

20. Heinrichs WL, Climie ARW, Cook JC: Cure of primary mesodermal mixed tumor by radiotherapy. Obstet Gynecol 19:537-541, Apr 1962

21. Rachmaninoff N, Climie ARW: Mixed mesodermal tumors of the uterus. Cancer 19:1705-1710, Nov 1966

22. Chaves E: Malignant mesodermal mixed tumors of the uterus—Report of 3 cases one of which associated with squamous cell carcinoma of the cervix and schistosomiasis of the uterine wall. Am J Obstet Gynecol 96:1017-1021, Dec 1, 1966

23. Norris HJ, Roth E, Taylor HB: Mesenchymal tumors of the uterus—II. A clinical and pathologic study of 31 mixed mesodermal tumors. Obstet Gynecol 28:57-63, Jul 1966

24. Mendel EB, Lucas WF, Panopio I: Malignant mixed mullerian tumors of the uterus. Obstet Gynecol 30:66-69, Jul 1967

25. Persaud V, Knight LP: Malignant mesenchymal tumours of the corpus uteri. West Indian Med J 17:96-102, Jun 1968

26. Gudgeon DH: Mixed mesodermal tumour of the uterus occurring after radiotherapy. Proc Roy Soc Med 61:1281, Dec 12, 1968

27. Ruffolo EH, Metts NB, Sanders HL: Malignant mixed mullerian tumors of the uterus—A clinicopathologic study of 9 patients. Obstet Gynecol 33:544-552, Apr 1969

28. Masterson JG, Kremper J: Mixed mesodermal tumors. Am J Obstet Gynecol 104:693-698, Jul 1, 1969

29. Edwards CL: Undifferentiated tumors, *In* Cancer of the Uterus and Ovary. 11th Clinical Conference on Cancer, M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Chicago, Year Book Medical Publishers Inc, 1969. pp 84-94

30. Glover JB: Mixed mesodermal tumors—Report of a case. North Carolina Med J 31:461-462, Dec 1970

31. Reddy DJ, Bharma T, Sankaran V, et al: Corporeal mesodermal mixed tumours of the uterus. J Indian Med Ass 54:153-157, Feb 16, 1970

32. Schaepman-Van Guens EJ: Mixed tumors and carcinosarcomas of the uterus evaluated five years after treatment. Cancer 25:72-77, Jan 1970

33. Giarratano RC, Slate TA: Sarcomas of the uterus. Obstet Gynecol 38:472-477, Sep 1971

34. Czernobilsky B, Labarre GC: Carcinosarcoma and mixed mesodermal tumor of the ovary—A clinicopathologic analysis of 9 cases. Obstet Gynecol 31:21-32, Jan 1968

35. Saunders P, Price AB, Taylor RW: Mixed mesodermal tumour of the ovary arising in pelvic endometriosis. Proc Roy Soc Med 63:1050-1051, Oct 1970

36. Sternberg WH, Clark WH, Smith RC: Malignant mixed müllerian tumor (mixed mesodermal tumor of the uterus). Cancer 7:704-724, Jul 1954

37. Aaro LA, Symmonds RE, Dockerty MB: Sarcoma of the uterus—A clinical and pathologic study of 177 cases. Am J Obstet Gynec 94:101-109, Jan 1, 1966

38. Hill RP, Miller FN Jr: Combined mesenchymal sarcoma and carcinoma (carcinosarcoma) of the uterus. Cancer 4:803-816, Jul 1951

39. Marcella LC, Cromer JK: Mixed mesodermal tumors—A report of 11 cases. Am J Obstet Gynecol 77:275-285, Feb 1959

40. Rubin A: The histogenesis of carcinosarcoma (mixed mesodermal tumor) of the uterus as revealed by tissue culture studies. Am J Obstet Gynecol 77:269-274, Feb 1959

41. Lebowich RJ, Ehrlich HE: Mesodermal mixed tumors of corpus uteri—Report of a case with review of the literature. Surgery 10:411-433, Sep 1941

42. Murray MR: Cultural characteristics of three granular-cell myoblastomas. Cancer 4:857-865, Jul 1951

43. Pogogeff IA, Murray MR: Form and behavior of adult mammalian skeletal muscle in vitro. Anat Rec 95:321-335, May 1946

44. Williams TJ, Woodruff JD: Similarities in malignant mixed mesenchymal tumors of the endometrium. Obstet Gynecol Surv 17:1-18, Feb 1962

45. Carter ER, McDonald JR: Uterine mesodermal mixed tumors. Am J Obstet Gynecol 80:368-373, Aug 1960

46. Vellios F, Stander RW, Huber CP: Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. Am J Clin Path 39:496-505, May 1963

47. Glass M, Goldsmith JW Jr: A review of 94 mixed mesodermal tumors of the uterus, with a report of an additional case. Am J Obstet Gynecol 41:309-317, Feb 1941

## Management of the Acute and Subacute Phases of Alcohol Abuse: Taking a Drinking History

The technique of taking a drinking history is a technique that you can develop. The technique is not, "Do you drink?", "How much do you drink?", "How often do you drink?" and "How long have you been drinking?" Those are all the wrong questions to ask. They're judgmental on the front end. You will never get a truthful answer . . . never.

There are some guidelines to taking a drinking history: First, you might as well assume that 70 percent of your adult population drink on somewhat more than a casual basis. You should begin to initiate the conversation by discussing the patient's *use* of alcohol, not his *abuse*. And the questions of "how much" and "how long" imply abuse on the front end.

You must convince the patient that alcohol is a drug, and he is self-prescribing the drug for the effect. Ask him about the effect he's looking for. Does he have the same effect every time he drinks? Is it taking a little bit more alcohol now? What is the social setting in which he takes alcohol? What is the relationship of alcohol to meals? And without asking him directly, how much, how often, how long, he will tell you. And if you can get a patient to tell you without asking him, then you have become a good drinking historian. Be as non-judgmental and non-moralistic as possible in taking the history; and the whole point of taking the history is to find out how important alcohol is to this individual . . . Begin to appreciate that alcohol is indeed involved probably in a lot more medical disorders than you have previously suspected . . . You occupy a very critical position in directing the health care of this individual if indeed he is addicted to alcohol and if indeed he needs more help than this. So the physician really does stand at a unique vantage point in making an early diagnosis and intervening early in a treatment situation. And if we do this, then we are operating at the best secondary level of preventive medicine. That's early intervention and early treatment. And if we do this, then I think we will indeed make an impact on the public health problem that's going to get a lot worse before it gets any better.

—David H. Knott, MD, *Memphis*

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