Primary Mesenteric Malignant Mixed Mesodermal (Müllerian) Tumor with Neuroendocrine Differentiation

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Extragenital malignant mixed mesodermal (müllerian) tumors (MMMT) are rare neoplasms, with but 24 well documented cases in the literature. Neuroendocrine differentiation in mixed müllerian neoplasms has been mentioned only anecdotally. We report on the clinical, pathological, and immunohistochemical features of a hitherto-undescribed extragenital MMMT with prominent neuroendocrine differentiation arising from the jejunal mesentery. This lesion was composed of a poorly differentiated epithelial component and a spindle cell component with heterologous (rhabdomyoblastic) differentiation. The bulk of the tumor consisted of small cell neuroendocrine carcinoma, which exhibited strong immunoreactivity for NSE, LEU-7, chromogranin A and synaptophysin. Electronmicroscopy confirmed the presence of neurosecretory dense-core granules. The primary mesenteric origin of the tumor was established at autopsy. Along with a brief review of previously reported extragenital MMMT some histogenetic concepts relevant to this case are discussed.

KEY WORDS: Extragenital malignant mixed müllerian tumor, Mesentery, Neuroendocrine differentiation.

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Primary peritoneal neoplasms composed of both malignant epithelial and stromal elements have variously been referred to as extragenital malignant mixed mesodermal tumors (1–5), malignant mixed müllerian tumors (6–18), carcinosarcomas (19–21) and mixed tumors of müllerian type (22–24). This lack of consistent terminology reflects both the rarity of these lesions, mostly described in single case reports, as well as the uncertainties concerning the histogenesis. An extensive small cell neuroendocrine carcinoma component in a primary extragenital MMMT has never been documented before.

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CASE REPORT

A 78-year-old woman was admitted to the hospital complaining of diffuse abdominal pain, nausea, anorexia and dyspnea and loose bowel movements. Abdominal examination revealed a large abdominal mass, corresponding to a subomental predominantly solid, partially cystic tumor on abdominal ultrasound and computerized tomograph. Chest X-ray was normal. This nulligravid patient recalled the removal of a benign endocervical polyp 45 years earlier; other than this there was no remarkable gynaecological history. Urgent laparatomy revealed and totally resected a bleeding abdominal tumor, measuring 16 cm in maximal dimension, attached to the jejunal mesentery and involving a mesenteric lymph node. The rest of the abdominal cavity, including ovaries, fallopian tubes and uterine corpus was normal. The postoperative course was unremarkable. No chemotherapy was started, in view of the overall poor medical condition of the patient. Approximately one month after surgery, ultrasound revealed multiple large (up to 10 cm) peritoneal nodules. The patient died shortly after admittance. Autopsy revealed the presence of innumerable peritoneal tumor nodules involving the visceral and parietal peritoneum. No primary tumor was found.

Pathologic Findings

Gross Appearance

The initial surgical specimen consisted of mesenteric tissue, diffusely invaded and markedly distorted by a soft, friable 16 × 13 × 8 cm tumor (Fig. 1). This tumor was predominantly solid, partially cystic. Firm, tan nodules were intermingled with areas of hemorrhage.

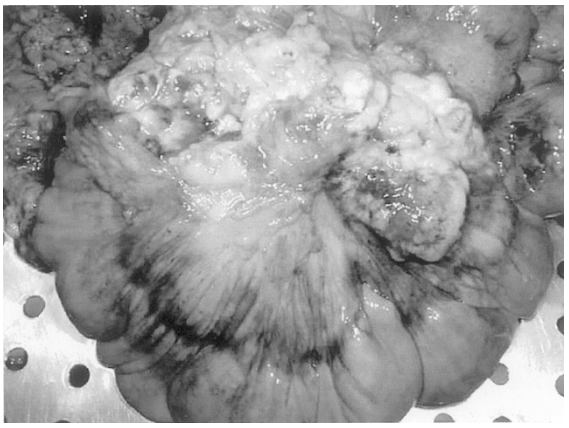

FIGURE 1. Jejunal mesentery with bulging tumor mass.

Light Microscopic Appearance

Light microscopy showed a tumor with a biphasic pattern. The larger part of the tumor consisted of sheets, cords and nests of poorly differentiated small to intermediate-sized cells with scant, ill-defined cytoplasm and hyperchromatic nuclei (Fig. 2). Numerous perivascular pseudorosettes were present. Most nuclei displayed an evenly dispersed chromatin pattern, with inconspicuous nucleoli. There was prominent nuclear molding, along with single-cell necrosis and a high mitotic rate. Scattered throughout this small cell component, trabeculae, sheets and glandular structures composed of larger cells with more prominent amphophilic cytoplasm, focally resembling endometroid adenocarcinoma, were present (Fig. 3). The sarcomatous areas consisted of spindle cells with oval or pleomorphic nuclei, focally arranged in bundles, mostly with a haphazardous architecture. Pleomorphic giant cells were conspicuous in some areas. Mitoses were plentiful, most of them atypical. The peritoneal nodules examined postmortem consisted mainly of the small cell component, with multinuclear giant cells scattered throughout. There was no evidence of endosalpingiosis or endometriosis. Multiple blocks from the ovaries, uterus and cervix were examined, none showed evidence of malignancy.

Immunohistochemistry

Immunohistochemistry was performed on formalin-fixed and paraffin-embedded tissue utilizing the avidin-biotin complex method, with a panel of immunohistochemical markers comprising cytokeratin (1:50; Immunotech), desmin (1:10; Boehringer), chromogranin A (1:100; Argene-Biosoft), Leu-7 (1:10; Bectondickinson), myogenin (1:30, Novocastra),

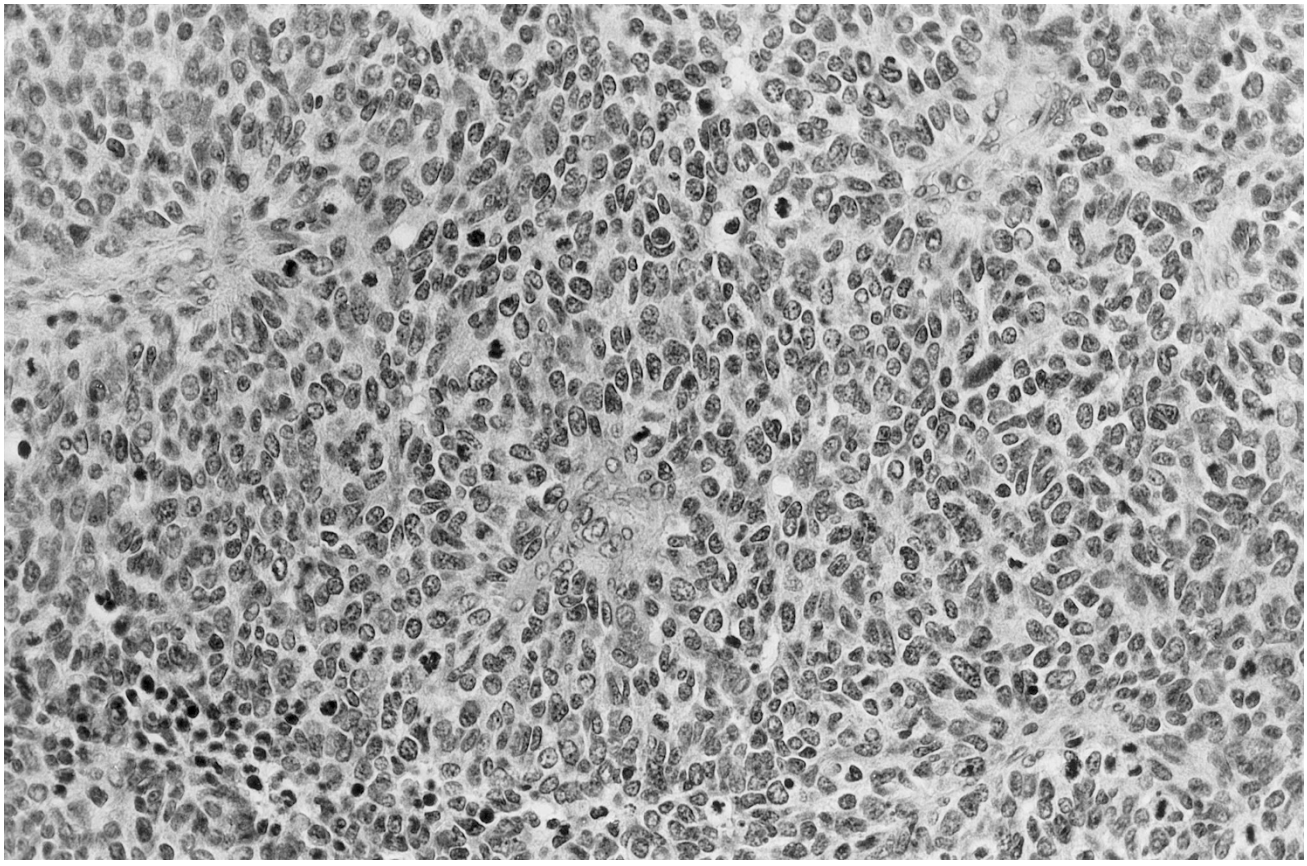

FIGURE 2. Small cell carcinoma component. Note perivascular pseudorosetting and multiple mitotic figures. These cells showed dot-like positivity for epithelial markers and strongly expressed all neuroendocrine markers (hematoxylin and eosin).

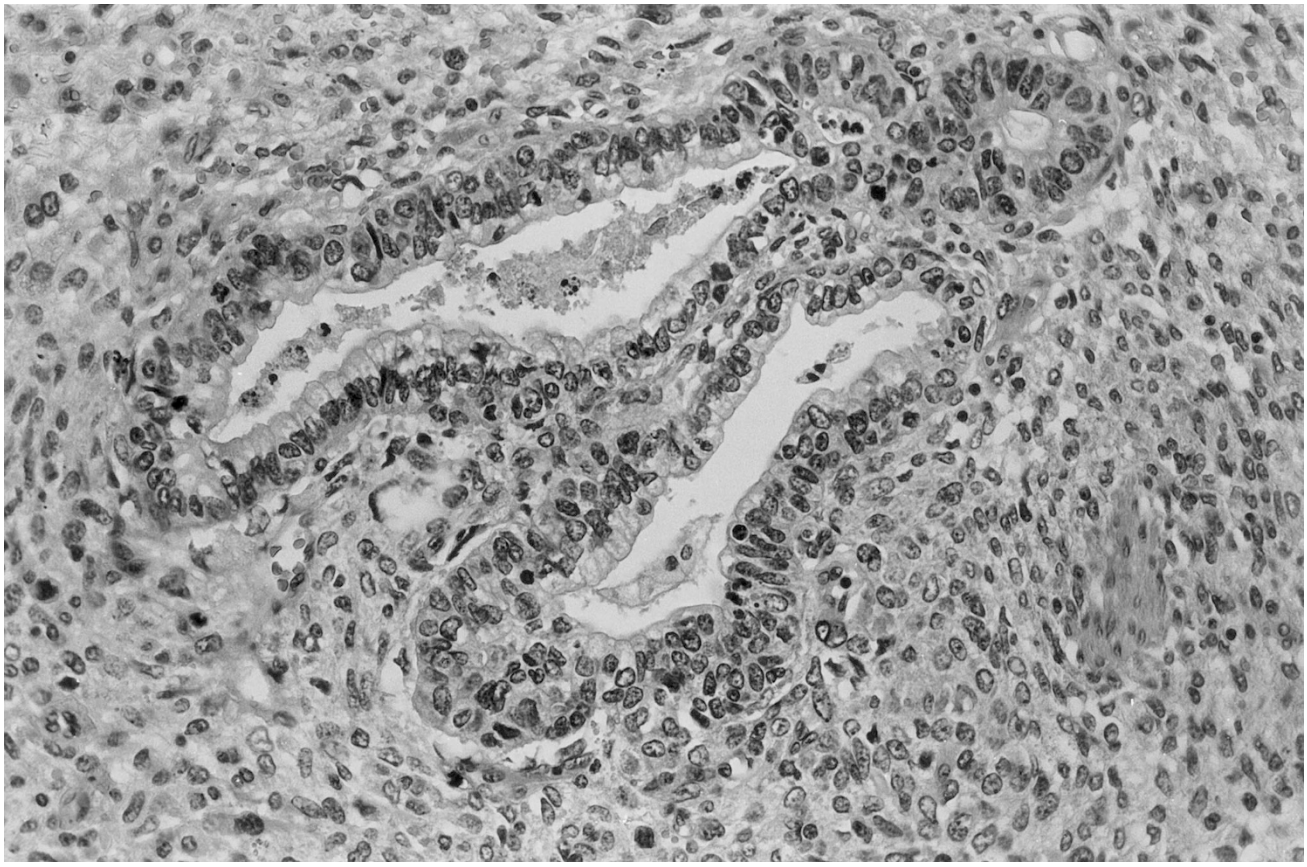

FIGURE 3. Biphasic pattern, with endometrial-like glands surrounded by a highly cellular and mitotically active spindle cell component (hematoxylin and eosin).

LCA (Leukocyte Common Antigen, 1:50), CD99 (MIC-2, 1:200), alpha smooth muscle actin (1:40), epithelial membrane antigen (1:100), BerEP4 (1:10), cytokeratin 7 (1:50), vimentin (1:40), synaptophysin (1:50), neuron specific enolase (1:200) (all antibodies from Dakopatts, Glostrup, Denmark, unless otherwise specified). It highlighted a previously unsuspected rhabdomyosarcomatous component, with sheets of small spindled and larger, tadpole-like cells staining for desmin and myogenin. The small cell component proved to be of an epithelial nature, with dot-like positivity of the tumor cells for EMA, keratin and BerEP4. Stains for LCA and CD99 were uniformly negative. There was strong and consistent expression of chromogranin A, synaptophysin, NSE and Leu-7. Much to our surprise, this neuroendocrine phenotype was maintained throughout a large part of the sarcomatous component (Fig. 4). The sarcomatous component strongly expressed vimentin, while no definite positivity for epithelial markers was noted. The abovementioned larger cyst-like spaces were lined by a conspicuous layer of BerEP4 negative, CK7 and vimentin positive flattened cells, with oval to spindle shaped nuclei.

Electron microscopic examination revealed some dense-core neurosecretory granules in all tumor components, confirming the neuroendocrine features suggested by immunohistochemistry.

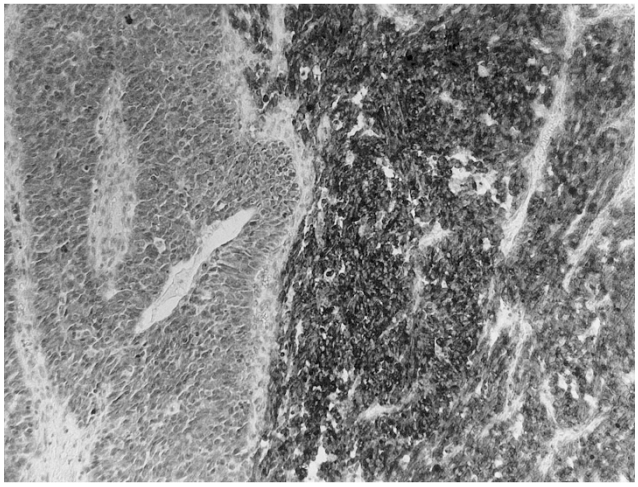

FIGURE 4. Synaptophysin stain. Note faint positivity in the epithelial component (*left) and strong staining of the spindle cell component* (right). This spindle cell component expressed vimentin, and was negative for all epithelial markers.

DISCUSSION

The peritoneal surfaces are host to a range of benign and malignant lesions commonly encoun-

tered in the müllerian duct derivatives of the female genital tract (25). This remarkable müllerian potential of the peritoneal mesothelium and adjacent mesenchyme reiterates its shared mesodermal ancestry with the primary müllerian sytem, wich derives from invaginated coelomic epithelium. These lesions from the so-called "secondary müllerian system," a term coined by Lauchlan in 1972 (26), are not restricted to the female peritoneum, since similar neoplasms have been described in men (27). Primary peritoneal müllerian tumors have been hypothesized to arise either from foci of endometriosis (8, 19), from müllerian duct remnants (21) or directly from the mesothelium and submesothelial mesenchyme, through a proces of metaplasia (23, 26, 28, 29).

Primary peritoneal malignant mixed mesodermal tumors (MMMT), similar to their more frequent counterparts in the uterus, fallopian tubes and cervix, are rare neoplasms. Not including MMMTs arising from the specialized ovarian surface epithelium (differing from the extraovarian peritoneal surface epithelium on a histochemical, enzymatic, biological and immunohistochemical level (30)), 24 examples of these tumors can be found in the literature, some of which could be questioned as to their primary peritoneal nature. In addition, 2 cases originating from the peritoneum were included in a large review on immunohistochemical properties of MMMTs, but were not amenable to proper analysis (24).

None of these tumors exhibited neuroendocrine differentiation, with the notable exception of a recent example arising in the cecal wall, where occasional epithelial cells stained for chromogranin (18). The neoplasm we report showed prominent neuroendocrine differentiation, including an extensive small cell neuroendocrine carcinoma component, with strong and consistent positivity for chromogranin A, synaptophysin, NSE and Leu-7. These findings could have been anticipated, in keeping with the Lauchlan theory, since, although sparsely mentioned, neuroendocrine differentiation has been recognized in uterine MMMTs (24, 31–33), as it has recently in an ovarian example (34). Some of these uterine MMMTs featured a small cell neuroendocrine carcinoma component, analogous to their infamous counterparts in the lung (32).

Extra-pulmonary small cell neuroendocrine carcinomas have been reported to occur in a variety of organs, such as the gastrointestinal system, paranasal sinuses, salivary glands, larynx, thymus, breast, prostate and genitourinary system (35, 36). Recently, a large single institutional series included one pelvic peritoneal example in a female patient (37). No detailed information regarding other possible primaries (especially female genital tract) or postmortem autopsy findings were available however.

Entities to be considered in the differential diagnosis in the present case include the intrabdominal desmoplastic small round cell tumor (DSRCT), a primitive neuroectodermal tumor (PNET) or a so-called small cell mesothelioma (38–42). These diagnoses are highly unlikely however, in view of the advanced age of the patient and the characteristic morphological and immunohistochemical features of this tumor.

Over the last decade, evidence from molecular genetic studies has accumulated towards a histogenetical epithelial-to-mesenchymal transformation mechanism of histogenesis for MMMT (43–46). This "conversion hypothesis" implies a common stem cell precursor with two phenotypically different tumor cell populations diverging at a rather late stage in clonal evolution (43). These data complement initial clinical, histological, immunohistochemical and ultrastructural studies (44, 47–51), leading to the current view that these tumors should be regarded as "sarcomatoid" or "metaplastic" carcinomas, and treated accordingly (52).

A multipotent progenitor cell residing in the mesothelium or adjacent mesenchyme has been implicated in the histogenesis of both desmoplastic small round cell tumors (DSRCT) and mesotheliomas (38, 53, 54). Both of these neoplasms have been shown to coexpress keratin, vimentin, desmin and, interestingly, sometimes even neural markers such as NSE, Leu 7, chromogranin and synaptophysin. The phenotypical diversity of extragenital MMMTs suggests a similar origin from progenitor cells within the mesothelium, with multidirectional differentiation (23).

In view of this "conversion hypothesis," the actual number of primary peritoneal MMMT may be even less than reported. Several cases occurred either metachronously or synchronously with ovarian and/or uterine endometroid adenocarcinoma or serous papillary carcinoma (6, 7, 9, 11, 18, 19, 22). Metastasis with epithelial-to-mesenchymal transformation seems an equally defendable explanation in these cases, being more likely than the co-occurrence of 2 independent malignant tumors.

The multiple cyst-like spaces present in the tumor, most of which were lined by flattened cells with the immunohistochemical properties of mesothelium, could be interpreted as multifocal differentiation of tumor cells towards a mesothelial-like phenotype. This phenomenon reiterates the bewildering interplay between peritoneal Mullerian-type epithelial neoplasms and the mesothelial progenitor cells from which they seem to originate.

In summary, we report on a primary mesenteric neoplasm, exhibiting both carcinomatous and sarcomatous features, with a small cell carcinoma

component and prominent neuroendocrine differentiation. The latter feature, suggesting a monoclonal origin in being expressed by all tumor components, lends further support to the "conversion hypothesis" regarding the histogenesis of MMMT.

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