Adenocarcinoid of the Appendix Presenting with Metastases to the Liver

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A case of hepatomegalia due to multiple metastases of unknown origin to the liver is described. At autopsy the primary tumor, an adenocarcinoid tumor of the appendix, was identified along with multiple metastases to the lymph nodes and widespread peritoneal carcinoidosis. Hepatic metastases from an appendiceal adenocarcinoid tumor has not been described previously. In the liver and lymph nodes the tumor had an insular growth pattern and was composed predominantly of cells of carcinoid type, whereas the carcinoidosis was composed almost entirely of signet-ring cells. It is suggested that differentiation of the metastases of appendiceal adenocarcinoids is modulated by factors in the recipient organ. [Key words: Adenocarcinoid of appendix; Liver metastasis; Peritoneal carcinoidosis]

ADENOCARCINOID OF THE appendix is a rather infrequently occurring tumor that also has been designated variably as mucinous carcinoid,[1] goblet-cell carcinoid,[2] or crypt-cell carcinoma.[3] When metastatic spread occurs, it shows a predilection for the peritoneum and ovaries.[4-7] A patient who presented with metastases to the liver and lymph nodes as well as to the peritoneum is reported.

Report of a Case

A 74-year-old woman was admitted with a diagnosis of occult cancer. Three weeks prior to admission she complained of pain in the right iliac fossa, nausea, anorexia, and minor weight loss. She had no episodes of flushing or diarrhea. Oppression behind the sternum nine months previously had resulted in an x-ray examination of the esophagus and stomach, with negative results.

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Physical examination revealed an enlarged, firm, nodular liver and a slight degree of jaundice. Liver enzymes and serum bilirubin were elevated, but serum chemistries, hemogram, and urinalysis were essentially normal. Ultrasonography revealed a greatly enlarged liver with multiple metastases. The condition of the patient declined rapidly and she died within two weeks admission.

Pathology: Post-mortem examination revealed an appendix that was transformed into a firm, pale, tumor mass with a diameter of 3 cm. Both fallopian tubes were thickened, measuring 1.5 cm in diameter. The ovaries and uterus appeared normal. The liver was enlarged, measuring 30 × 25 × 9 cm, and massively infiltrated with large tumorous deposits, leaving only small amounts of normal-appearing liver parenchyma. Several enlarged lymph nodes were found in the ileocecal region and upper abdomen. Eight hundred milliliters of ascitic fluid was present.

Tissue from the gross specimen was fixed in ten percent neutral buffered formalin and processed routinely for light microscopy. Sections were stained with hematoxylin and eosin, PAS-alcian blue pH 2.7, Grimelius' stain, Masson-Fontana's stain, and immunoperoxidase stains for neuron-specific enolase and serotonin.

Examination of the appendix revealed tumor infiltration in all layers of the wall, extending into the mesoappendix. The tumor was composed of tubuloglandular structures and strands of tumor cells that were mainly of the signet-ring type (Fig. 1). A smaller number

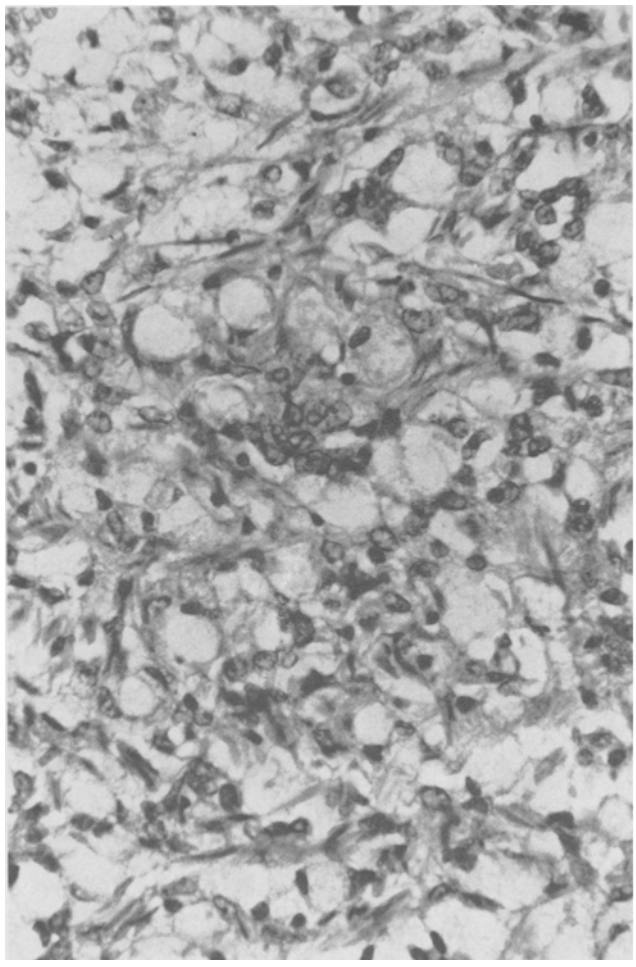

FIG. 1. Adenocarcinoid of appendix composed predominantly of signet-ring cells (hematoxylin and eosin; × 300).

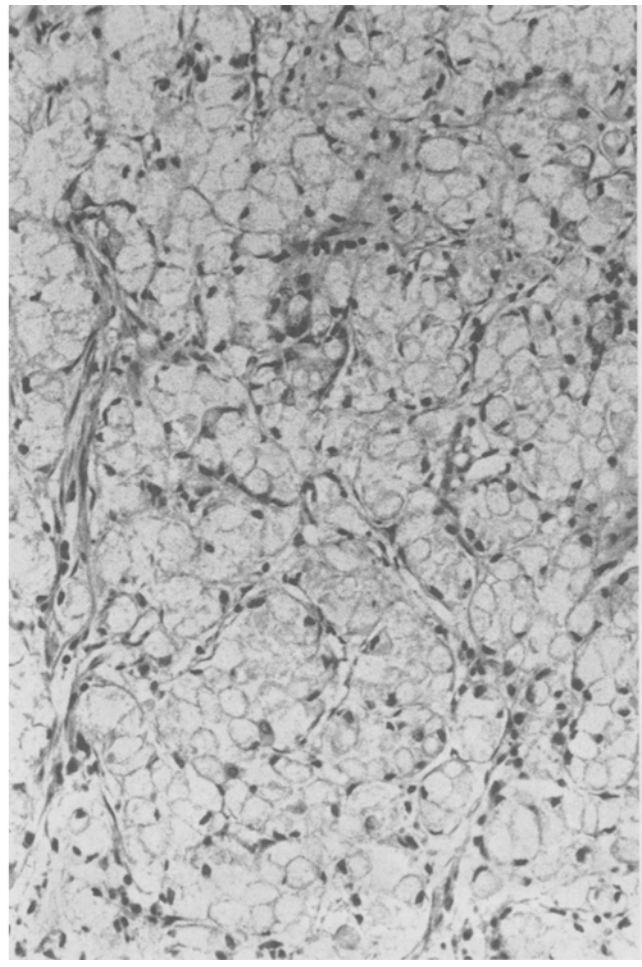

FIG. 2. Carcinoidosis from colon which, in this area, is composed entirely of signet-ring cells (hematoxylin and eosin; × 175).

of cells with a more scanty, basophilic cytoplasm were scattered between the signet-ring cells. There was a slight nuclear atypia with small nucleoli. Mitotic figures numbered two to four per ten high power fields. Perineural and lymphatic invasion in the mesoappendix were conspicuous features.

Areas of carcinoidosis were found in sections from the ovaries, fallopian tubes, uterus, and colon. The histology differed from that of the appendiceal primary in that large areas were composed entirely of diffusely infiltrating signet-ring cells without cells of the typical carcinoid type (Fig. 2).

The metastases to the liver and lymph nodes, however, showed an insular pattern typical of midgut carcinoids. The islands were composed of signet-ring cells centrally, surrounded by cells of the carcinoid type, which predominated (Figs. 3 and 4). Blood vessel invasion was seen in the liver (Fig. 5).

Argyrophil granules could be found in small numbers in the primary tumor as well as in the secondary deposits. Stains for argentaffin granules, neuron-specific enolase, and serotonin were negative in the appendix as well as in the metastases.

Discussion

Carcinoid tumors are the most frequently occurring neoplasms of the vermiform appendix and are found in 0.06 to 0.69 percent of appendectomies.[1] The metastatic ability is low in spite of the fact that invasion into the muscular layer is a common finding.[8-11] Lymph-channel and perineural invasion are found commonly also.[8-10]

The most common metastatic sites are the regional lymph nodes. In 1968, Moertel *et al.*[8] collected reports from the literature of 35 cases of appendiceal carcinoid tumors with metastases (including two of their own). In 19 of these cases, the involvement was of regional nodes only, in four regional nodes plus the right ovary were involved, and in 12 there was widespread metastatic malignant disease.

Development of the carcinoid syndrome requires large

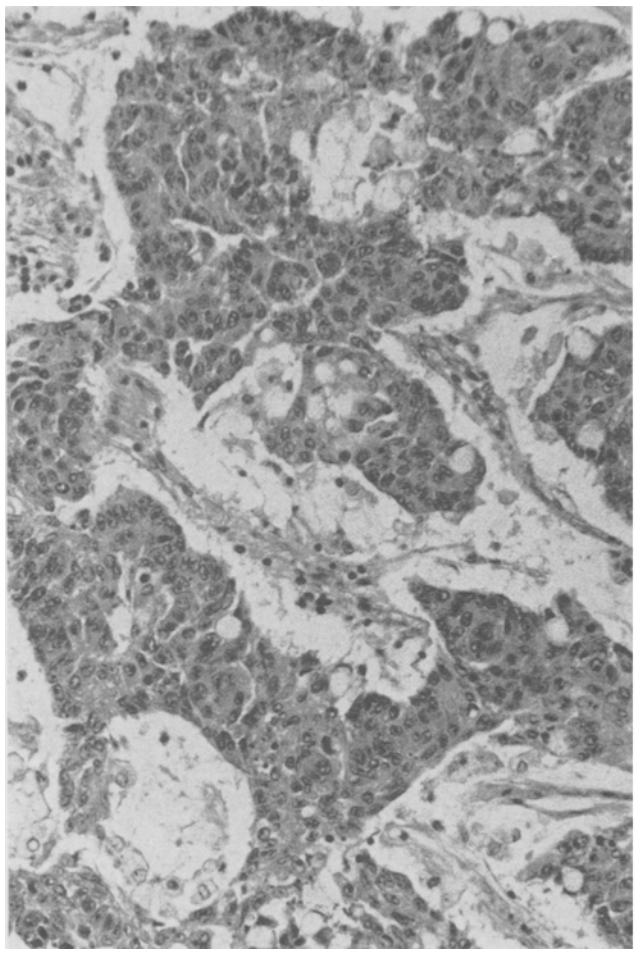

FIG. 3. Liver metastasis showing an insular growth pattern. The tumor is composed of a mixture of signet-ring cells and cells of carcinoid type (hematoxylin and eosin; × 175).

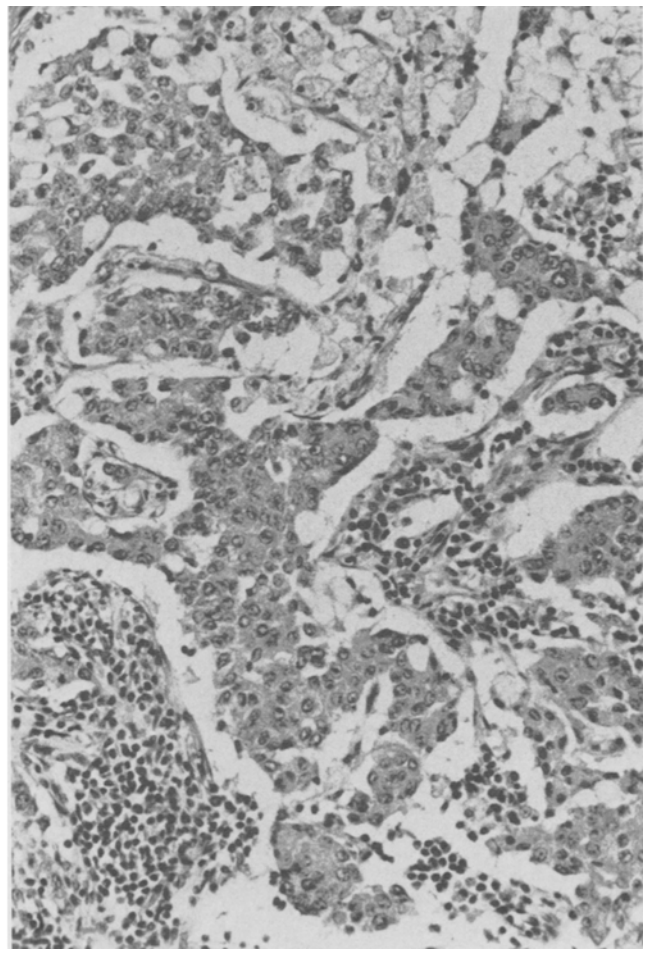

FIG. 4. Lymph-node metastasis with the same composition as the liver metastasis (hematoxylin and eosin, × 175).

tumorous deposits usually, but not necessarily, in the liver.[12] Moertel *et al.*[8] found five cases of carcinoid syndrome, including a case of their own.

Adenocarcinoids share the histologic features of both carcinoid tumors and adenocarcinomas. They usually are regarded as a variant of the conventional carcinoids, although some authors prefer to include them among the carcinomas.[3,13] In the early reports[1,2,14] the malignant potential of the adenocarcinoids was found to be comparable to that of conventional carcinoids. It has now become apparent, however, that these composite neoplasms behave more aggressively that the conventional carcinoids.[4,5,13,15] Furthermore, their metastatic pattern is different, with peritoneal carcinoidosis as the predominant manifestation. Bilateral ovarian metastases are found in about half of the cases[5-7] associated, in most instances, with widespread peritoneal involvement. Lymph-node metastasis has been described in only four cases.[4,13,15] Liver metastasis from appendiceal adenocarcinoids has not been described previously in the English medical literature, nor has the carcinoid syndrome.

In the present case, massive involvement of the liver was found. The metastatic tumor was similar to the primary appendiceal tumor, composed of a mixture of signet-ring cells and cells resembling a typical carcinoid tumor. The authors were unable to demonstrate argentaffin granules or the presence of neuron-specific enolase or serotonin by immunoperoxidase techniques, either in the primary tumor or in the secondary deposits, but this may be attributed to a suboptimal preservation of this kind of reactivity in autopsy material. The patient had no signs or symptoms of the carcinoid syndrome but, unfortunately, plasma serotonin or urinary 5-HIAA levels were not measured.

Recently Hirschfield *et al.*[5] reported a case of appendiceal adenocarcinoid with bilateral ovarian metastases. They found immunoreactivity for serotonin in the primary tumor, but not in the metastases, and concluded that the mucinous component might have a selective ability to metastasize.

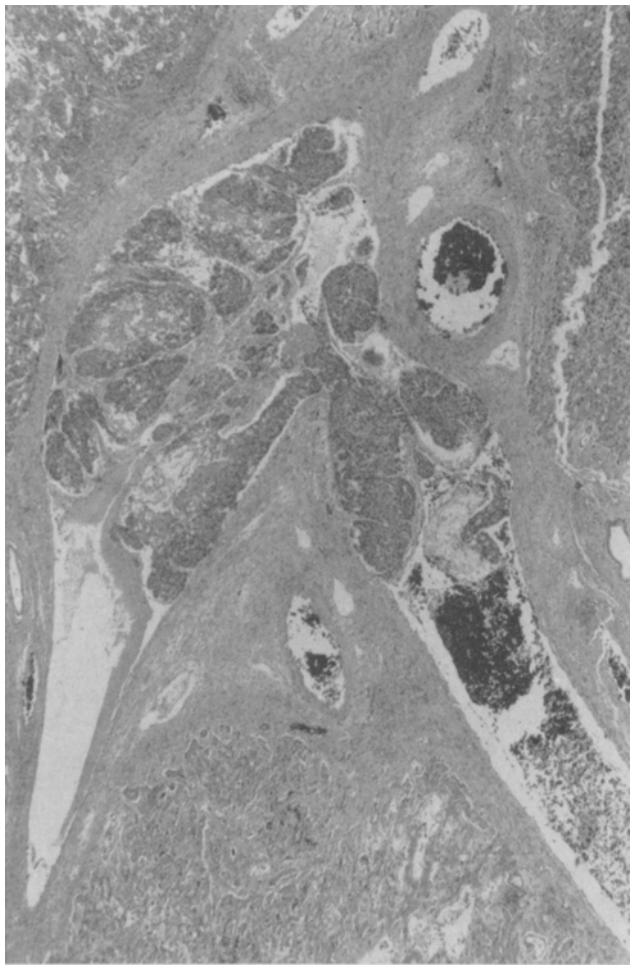

FIG. 5. Tumor embolus within a vein in the liver (hematoxylin and eosin; × 25).

On the contrary, Hood *et al.*,[7] in a similar case, found evidence of bidirectional differentiation in the ovarian metastases.

This case bears a certain similarity to that of Hirschfield *et al.*[5] in that large areas of the peritoneal carcinoidosis were composed entirely of signet-ring cells. On the other hand, there was light microscopic unequivocal evidence of a bidirectional differentiation with a predominance of the carcinoid cell type in the lymph nodes and liver.

It is intriguing that predominance of signet-ring cells is found in sites often involved by metastatic signet-ring cell carcinomas of the gastrointestinal tract, whereas predominance of the carcinoid cell-type is found in sites most often involved by metastasis of conventional carcinoid tumors of the appendix. This might suggest that differentiation of metastases from these tumors is determined not only by factors in the tumor cells, but is modulated by the recipient organ.

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