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Histopathology of locally advanced colorectal carcinoma, with emphasis on tumor invasion of adherent peritoneal membranes

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ABSTRACT

Locally advanced colorectal carcinomas are characterized by neoplastic cells that invade beyond the colon and directly into surrounding organs and structures that include the retroperitoneum and abdominopelvic sidewall. These aggressive tumors are prognostically adverse and are categorized with highest possible tumor stage in current cancer staging systems. Recognizing colorectal carcinoma with extensive locoregional invasion is typically straightforward, but some cases can be diagnostically challenging. These include tumors with limited invasion of extracolonic tissue such as the subserosa in which there are no cells or structures that are histologically or architecturally distinct from the colonic primary. Tumor-associated injury of the colonic peritoneum often precedes invasion by the neoplastic cells and can cause the peritoneal membrane of the colon to adhere and subsequently fuse to the peritoneal membrane of a neighboring organ or structure, thereby creating a transperitoneal bridge through which a tumor can directly invade the adherent extracolonic tissue. Hence, locally advanced colorectal carcinoma can be narrowly defined by neoplastic cells that completely invade through the fused peritoneal membrane and into the subserosa of the adherent extracolonic tissue. The evaluation of tumor invasion of the fused peritoneal membrane, which is enhanced by the combined use of an elastic stain and an immunostain for pan-keratin, is essential for the proper staging of locally advanced colorectal carcinoma and its clinical management.

1. Introduction

It is widely acknowledged that colorectal carcinoma with advanced locoregional invasion is associated with worse clinical outcome and is staged accordingly with the highest possible pathologic tumor stage (i.e., pT4b) [1–4]. These neoplasms are characterized by tumors that directly invade past the confines of the colon and into surrounding tissues that include neighboring visceral organs, omentum, retroperitoneum, and abdominopelvic sidewall. Proper staging of aggressive tumors with extensive invasion beyond the colon is often made with relative ease and confidence [5]. Recognizing locally aggressive tumors with limited invasion of extracolonic tissue, however, can be diagnostically challenging.

Tumors that arise in peritonealized portions of the colorectum can directly invade extracolonic tissue when the colon harboring the malignancy adheres to a nearby organ or structure [6,7]. Peritoneal membranes, when injured, are prone to developing adhesions [8–10], and tumor-associated injury of the colonic peritoneum likely accounts for the tissue adhesion, but a pathology-based examination of this process in locally aggressive colorectal carcinoma has not been performed to date. In this study, the histopathologic changes in the peritoneal membranes of the colon and surrounding organs and structures associated with locally advanced colorectal carcinoma are examined. The salient features associated with partial and complete tumor transgression through the adherent and fused peritoneal membranes are characterized, the recognition of which would enhance the proper pathologic staging and treatment of locally advanced colorectal carcinoma.

2. Materials and methods

The study was approved by the Institutional Review Board of Swedish Medical Center and Providence Health and Services with waiver of patient consent for use of archived pathology material. 50 colorectal carcinomas that arose above the peritoneal reflection and resected with adjacent visceral organs and structures from 2007 to 2016 were reviewed. The concomitantly resected tissues extrinsic to the colonic primary included discontinuous portions of the colon, appendix,

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small intestine, stomach, pancreas, liver, gallbladder, spleen, uterus, ovary, fallopian tube, urinary bladder, and omentum, retroperitoneal soft tissue and organs that included the left adrenal gland and ureter, and abdominopelvic sidewall. The tissues were fixed in formalin, processed, and stained with hematoxylin and eosin (H&E), Verhoeff-Van Gieson (VVG), and an immunostain for pan-keratin as previously described [11]. The 50 tumors were composed of 11 that invaded into but not beyond the fused peritoneal membranes of the colon and extracolonic tissues (i.e., pT3), and 39 that invaded through the fused peritoneal membranes and into the extracolonic tissues of the surrounding organs, retroperitoneum, and abdominopelvic sidewall (i.e., pT4b).

3. Results

50 primary colorectal carcinomas that were resected en bloc with adherent organs and structures were examined for histopathologic changes associated with locally advanced tumor invasion. Tumors that invaded cells and structures that were histologically and architecturally distinct from the primary colonic site such as the mucosa and muscularis propria of adherent visceral organs, including discontinuous segments of the colon, retroperitoneal organs, and the skeletal muscle and aponeurosis of the abdominopelvic sidewall were readily recognized as locally aggressive and staged as pT4b (Fig. 1).

Tumor-associated peritoneal injury and healing, characterized by inflammation, increased vascularity, proliferation and expansion of the peritoneal stroma, and fibrinous exudate at the serosal surface (Fig. 2a) can cause the peritoneal membrane of the colon to adhere to the peritoneal membrane of a neighboring visceral organ, omentum, retroperitoneum, or abdominopelvic sidewall. Adhesion of the apposed peritoneal membranes and obliteration of the free serosal surfaces with loss of the mesothelial layer resulted in fusion of the adherent peritoneal membranes that occurred prior to invasion by neoplastic cells (Fig. 2b–d). The serosal membrane is devoid of fat, and fusion of the adherent peritoneal membranes resulted in a continuous band of variably thickened fibrous tissue interposed between the subserosal fibroadipose tissues of the colon and adherent organ or structure, delimited by the respective elastic laminae (Fig. 2b–d). Because serosal stromal cell expression of cytokeratin is observed in injured and healing peritoneal membranes, a transdifferentiating feature of peritoneal stromal cells that is not seen in stromal cells of the subserosa, immunohistochemical staining for pan-keratin further clarified the anatomic extent of the fused peritoneal membrane (Fig. 2d).

There were no morphologic features that distinguished between the peritoneal membranes of the colon and extracolonic tissue when fused. Therefore, locally aggressive colorectal carcinoma staged as pT4b was best defined by neoplastic cells that completely invaded the fused peritoneal membrane, and through the elastic lamina and into the subserosa of the adherent extracolonic organ or structure. By routine H &E, the elastic lamina was sometimes seen as a thick, clear, refractile serpiginous band (Fig. 2e) that separated the less compact and more pale connective tissue of the fused peritoneal membrane from the more dense and more eosinophilic tissue of the adherent subserosa (Fig. 2f–g). Whereas the surface of the peritoneum was smooth and lined by the mesothelium and the submesothelial fibrous tissue of the peritoneal membrane, the soft tissue margin of the adherent organ or structure was typically ragged and irregular with fat that extended to the resection edge (Fig. 2h).

Of the 50 cases of deeply invasive colorectal carcinoma, the 11 cases of pT3 colorectal carcinoma were characterized by tumors that partially invaded the fused peritoneal membrane without extension past the elastic lamina or invasion of the subserosa of the adherent organ or structure (Fig. 3a–c). In these cases, the neoplastic cells at the point of deepest invasion were surrounded by the keratin-expressing stromal cells of the fused peritoneal membrane (Fig. 3c). By contrast, the 39 cases of pT4b colorectal carcinoma showed complete tumor transgression through the fused peritoneal membrane with tumor cells invading past the elastic lamina and into the fat-containing subserosa of the adherent organ or structure (Fig. 3d–f). These cases were further corroborated by immunostains for pan-keratin that showed neoplastic cells invading beyond the keratin-expressing stromal cells of the fused peritoneal membrane and into the keratin-negative stroma of the subserosa of the adherent organ or structure (Fig. 3f).

4. Discussion

Colorectal carcinomas that invade surrounding organs and/or structures, including the retroperitoneum and abdominopelvic sidewall, are locally aggressive tumors that are staged as pT4b in the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) cancer staging classifications [2,3]. These tumors are associated with decreased survival and comprise a subset of node

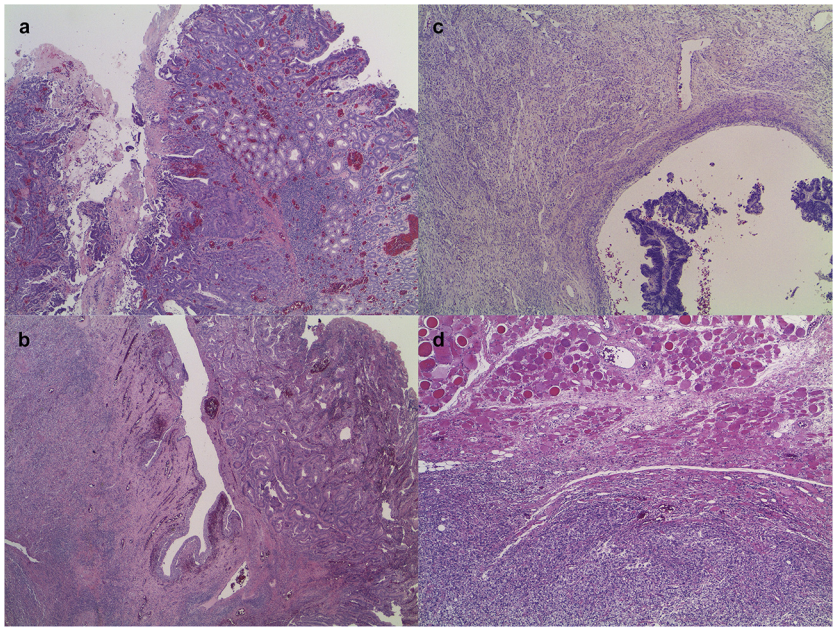

Fig 1. Locally advanced colorectal carcinoma with invasion of histologically distinctive extracolonic cells and structures (H&E). Colorectal carcinoma that invades cells and structures histologically and architecturally distinct from the primary colonic site is unequivocally recognized and staged as pT4b. These include (a) the villi and Brunner glands of duodenal mucosa, (b) urothelium of bladder mucosa, (c) the densely cellular spindle stromal cells of ovary, and (d) skeletal muscle of abdominopelvic sidewall.