NEOPLASMS

Adenocarcinoma, Colon and Rectum, Rat

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Synonyms. Colon carcinoma, rectal carcinoma, cancer of the large bowel

Gross Appearance

Spontaneous tumors of the colon are such rare events in rats and mice that little knowledge about them is available. Several carcinogens, to be described, have been used to induce malignant tumors in the colon and rectum of rats and mice. It is these induced neoplasms that will be considered. Each of these carcinogens produces a similar and predictable series of sequential changes leading to polypoid tumors (Fig. 384), often associated with an intussusception (Fig. 385), and sessile tumors (Fig. 386), the latter are often mucinous and locally invasive and may metastasize to mesenteric nodes, liver, and lung.

As indicated in Fig. 387, tumors arise in greatest numbers in the distal colon but can occur throughout the colon, particularly if a relatively large dose of carcinogen is administered. In the rat, the invasive mucinous adenocarcinomas tend to be localized in the proximal colon (Nauss et al. 1983; Takemiya et al. 1982), while polypoid tumors are found distally.

Microscopic Features

The earliest lesions appear at or near the mucosal surface as dysplastic glands with abnormal segments of gland continuing in direct apposition with the morphologically normal portion of the gland (Fig. 388). These progress to larger areas with neoplastic glands intermixed with normal-appearing glands (Fig. 389). They are later drawn up into polypoid structures (Fig. 390), some of which exhibit invasion of the stalk (Fig. 391). In rats, the localization of mucinous colon tumors over lymphoid aggregates (Fig. 392), has been recognized for 10 years (Rogers et al. 1973; Bland and Britton 1984) and recently has been documented in detail. Often, the earliest dysplastic mucosa is found over an aggregate (Nauss et al. 1984). Similar localization has been reported in mice (Wargovich et al. 1983).

The sessile-type adenocarcinomas in rats may produce little mucin; they have well-developed glands and grow exophytically. More often, they develop in the submucosa and are comprised of large mucin-filled glandular structures (Fig. 393). Still others produce a large amount of mucin and are partially or entirely comprised of signet-ring cells with little or no gland formation (Fig. 394). The mucin-producing tumors tend to occur in rats given higher doses of 1,2-dimethylhydrazine (DMH) or azoxymethane (AOM) (Takemiya et al. 1982; Nauss et al. 1983). In both types of tumors and in dysplastic colon epithelium prior to tumor development, abnormalities of mucin synthesis and secretion are prominent.

Biologic Features

Natural History

Signs of developing tumors in rats may go undetected, but close daily observation of freshly voided feces will often reveal bright-red blood. Occult blood tests have not, in our hands, proven to be any better at detection than simple visual observations. The general clinical condition of the rat does not deteriorate until tumor development is well advanced; death may result from massive bleeding or obstruction. Clinical signs are of little help in estimating stage of tumor growth.

The colon epithelium over the lymphoid aggregates in normal rats appears equipped to take up and digest bacteria or other antigens present in the lumen; the antigens may be passed to the adjacent lymphoid cells for processing. Analogies can be
made to the small intestinal epithelium over Peyer’s patches (Bland and Britton 1984). It appears possible that this epithelium may differ metabolically from the epithelium in other colon segments. There may be differences in vascular supply to the colon segments that contain lymphoid aggregates, or the lymphoid tissue may modulate the development of intestinal tumors by secretion of lymphokines or by other interactions. An improved prognosis is associated with an active acute and chronic inflammatory response in human colon cancer (Braun and Harris 1981). This inflammatory response is, of course, histologically distinct from lymphoid aggregates and has not found a parallel in the rodent model, but further research may reveal an association.

Etiology

Two types of chemicals have been used to induce adenocarcinomas in the colon of rodents as models for the human disease. One type is the direct-acting (complete) carcinogen, which requires no metabolic activation. The two members of this group used by most investigators are methylnitrosourea (MNU) and methylnitronitrosoguanidine (MNNG). MNU is the more useful of the two; it can be given as a single dose or a small