Nodular Formations in the Rat Small Intestine after Local Abdominal X-irradiation

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SUMMARY

The abdomen of Wistar rats was irradiated locally with 1000 to 2000 rads. Approximately 2 months following irradiation, visible nodules were found in the intestines of the groups receiving irradiation. Nodule incidence was 80 to 100% in groups that received 1750 or 2000 rads, 50% in the 1500-rad groups, and 3% in the 1000-rad groups, respectively.

The histology of the nodules revealed adenomatous hyperplasia, including invasion of submucosa, muscle layers, and serosa of the small intestine accompanied by an area of fibrous tissue resulting from desmoplastic reaction by irradiation injury.

INTRODUCTION

Spontaneous intestinal tumors in rats and mice are very rare (1, 6, 7). Induction of carcinoma in the rat small intestine by ionizing irradiation has been reported by Osborne et al. (5); in mice, with fast-neutron irradiation, a high incidence of intestinal tumor was reported by Nowell et al. (3, 4).

These reports concern the postirradiation delayed-effect tumor incidence at late times but do not concern the process leading to actual tumorigenesis by irradiation. This process is important, however, for it relates to irradiation-induced tissue injury as a possible direct cause of tumorigenesis.

This paper reports quantitative induction of visible nodules in the small intestine within 2 months after various doses of irradiation, and the possibility of tumorigenesis in nodule formation is discussed.

MATERIALS AND METHODS

Male and female Wistar rats, 9 to 12 weeks old, weighing 200 to 400 g and fed ad libitum on a standard diet of pellets and water, were used for abdominal irradiation. Animals were anesthetized with an i.p. injection of Nembutal, 35 mg/kg, and the abdominal areas were shielded with a 3-mm lead plate in order to make a central irradiation area (3 x 0.8 cm) between the xiphoid process and coccyx, as shown in Chart 1. This target area included the jejunum and ileum of the small intestine and colon and excluded spleen, kidney, liver, large intestine, and stomach.

The irradiation factors used were 200 KVp, 20 ma, 0.5 mm Cu, and 0.5 mm Al filtration (half-value layer, 1.13 mm Cu). Dose rate measured in Mix-D phantom was 135 rads/min at a 1-cm depth in the abdomen. The doses were 1000, 1500, 1750, and 2000 rads. Between 50 and 70 days after the various doses of irradiation, all animals were sacrificed, whereupon visible nodules of the small intestine were detected. The subgroup at the 1750-rad dose was used for examination of nodule growth; the rats of the group were sacrificed 20 to 50 days after irradiation, and any nodules were then detected. For histological examination, visible nodules were fixed in 10% neutral formalin, embedded in paraffin, sectioned traversely at 6 µm, and stained with hematoxylin and eosin or periodic acid-Schiff stain. The size of the nodule was determined by measuring the maximum diameter of the nodule from the successively sectioned histological specimen.

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Chart 1. Irradiation procedures for rat.
Table 1

Incidence of small intestinal nodules in rat

<table>
<thead>
<tr>
<th>Exposure dose (rads)</th>
<th>Sex</th>
<th>No. of rats</th>
<th>No. of rats with nodules</th>
<th>No. of nodules</th>
<th>No. of nodules/rat</th>
<th>% incidence of nodule formation/rat</th>
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</thead>
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<tr>
<td>1000</td>
<td>F</td>
<td>29</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
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<td>1000</td>
<td>M</td>
<td>23</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
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<tr>
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<td>29</td>
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<td>44</td>
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<td>55</td>
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<tr>
<td>1500</td>
<td>M</td>
<td>11</td>
<td>5</td>
<td>14</td>
<td>2.8</td>
<td>45</td>
</tr>
<tr>
<td>1750</td>
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<td>14</td>
<td>37</td>
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<td>87</td>
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<tr>
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<td>15</td>
<td>12</td>
<td>28</td>
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</tr>
<tr>
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<td>F</td>
<td>27</td>
<td>24</td>
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<td>89</td>
</tr>
<tr>
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<td>12</td>
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<td>100</td>
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<td>26</td>
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</tbody>
</table>

* Rats were sacrificed 50 to 70 days after irradiation for the detection of nodules.

**RESULTS**

Fig. 1 shows a nodule detected in an animal 67 days after 2000 rads. Many such nodules were detected in the 1500-, 1750- and 2000-rad groups. The relationship between the dose and the incidence of nodule formation is summarized in Table 1. From Table 1, a dose of 1500 rads is seen to be the dose for a 50% incidence of nodule formation, and in the high (2000-rad)-dose group, a nodule incidence of nearly 100% was observed. The number of nodules per animal with nodules in each irradiated group was almost the same, except for the 1000-rad group. In the subgroup that received 1750 rads, nodule growth, as measured by the maximum diameter of traversed nodule sections, is summarized in Chart 2. Nodules grew gradually for 30 to 40 days after irradiation and then retained the same peak size thereafter. Fig. 2 shows the histology of the typical nodule. Nodules were composed of atypical glandular epithelial cells and of avascular fibrous tissue, as a result of the inflammatory reaction caused by ulceration following irradiation. The epithelial cells of the glandular tissue invaded the submucosal, muscular, and serosal layers. The invaded epithelial area occasionally showed adenomatous hyperplasia.

**DISCUSSION**

Irradiation-induced nodules in the rat intestine appeared to be irreversible both upon gross observation, as shown in Fig. 1, and upon histological observation, as shown in Fig. 2. Nodule growth began soon after irradiation (Chart 2). We assume that such nodule formations were caused by radiation injury of the stroma, epithelial glands of the mucosa, and muscular tissue. Consequently, a nodule is not strictly considered a tumor until 50 days after irradiation, but the observation of adenomatous hyperplasia in the atypical glandular tissue caused by the invasion of epithelial cells into submucosal, muscular, and serosal layers points up the possibility that a nodule might ultimately develop into adenocarcinoma. Therefore the process of nodule formation may very well be a condition that leads to tumorigenesis. Osborne et al. (5) also reported that formation of such a nodule, termed a tumor, was detectable 55 days after irradiation and that the histology of the nodule showed malignancy.

Details about the process and the mechanism involved in nodule formation must be clarified, and research toward this end is now under way.

**ACKNOWLEDGMENTS**

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**REFERENCES**

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Irradiation-induced Intestinal Nodules


Fig. 1. Nodule of small intestine detected at 67 days after 2000 rads of X-irradiation.
Fig. 2. Histology of nodule detected at 67 days after 2000 rads of X-irradiation. H & E, x 34.
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