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PARARENAL ANGIOSARCOMA AS A MANIFESTATION OF SEXUAL DIMORPHISM IN CARCINOGENESIS

V. S. Turusov and N. S. Lanko

UDC 616.615-006.31-092-055

Pararenal angiosarcomas appeared in 42% of male CBA mice receiving 1,2-dimethylhydrazine (DMH) subcutaneously in a dose of 8 mg/kg for 30 weeks. These tumors did not appear in any of the 176 female mice of the same line receiving DMH by the same scheme. Histologically the tumors were variants of angiosarcomas with marked invaive growth into kidney tissue.

KEY WORDS: carcinogenesis; angiosarcoma; sexual dimorphism; 1,2-dimethylhydrazine; tumor of the kidney.

The sex of an animal is known to influence the appearance of tumors developing through the action of various carcinogenic agents. The clearest example of this is the epithelial tumors of the kidneys which develop in male hamsters under the influence of diethylstilbestrol [4], but do not arise under the same conditions in females. In the same way, a higher frequency of epithelial tumors of the kidneys has been observed in male mice of the Swiss line receiving 1,2-dimethylhydrazine (DMH) than in females. In rats receiving DMH, sex-linked differences in the localization of epithelial tumors in different parts of the large intestine, disappearing after castration, have been described [1].

This paper describes an angiosarcoma of the pararenal cellular tissue developing under the influence of DMH in male mice only.

EXPERIMENTAL METHOD

Each of 50 male CBA mice receivied 30 subcutaneous weekly injections of DMH (8 mg/kg, calculated as base, in 0.3 ml distilled water). The injections were started at the age of 10-12 weeks. The mice remained under observation until natural death or sacrifice at 43-45 weeks after the beginning of the experiment. The dying or killed animals were autopsied and material obtained from them was fixed in 10% formalin and embedded in paraffin wax; sections were stained with hematoxylin-eosin.

EXPERIMENTAL RESULTS

In the 46 males which survived the minimal latent period tumors developed in the following situations: angiosarcomas of the pararenal cellular tissue in 20 (43%), epithelial tumors of the kidneys in five, tumors of the anal region in 28, the intestine in 15, and the liver in nine.

The first angiosarcoma in the pararenal cellular tissue was found in an animal which died 28 weeks after the beginning of DMH administration; most of these tumors were found after 35 weeks.

Laboratory of Carcinogens, Department of Carcinogenic Agents, Oncologic Scientific Center, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 7, pp. 74-75, July, 1979. Original article submitted March 5, 1979.

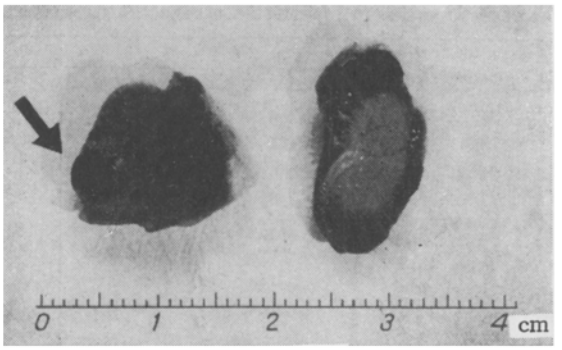

Fig. 1

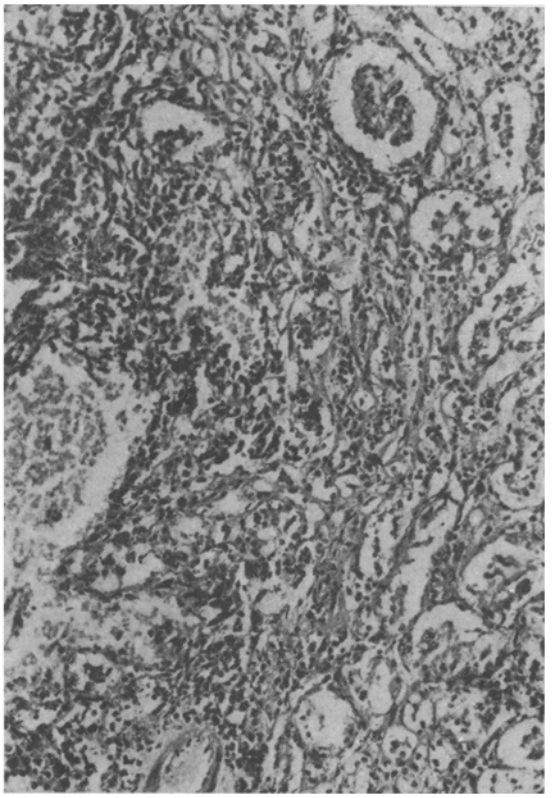

Fig. 2

Fig. 1. Pararenal angiosarcomas (external appearance). Left) a large tumor adherent to the kidney; another tumor can be seen in the kidney tissue (arrow). Right) the tumor covers the kidney like a capsule.

Fig. 2. Histological structure of angiosarcoma. The tumor (left) consists of small dark cells forming spaces filled with erythrocytes. Invasive growth into the kidney tissue can be clearly seen. Hematoxylin-eosin, 200×.

Macroscopically (Fig. 1) the small tumors (under 0.5 cm) had the appearance of hemorrhages into the renal capsule. Larger tumors spread over the whole kidney or one of its poles. In far advanced cases, large (up to 2-3 cm) dark red formations with a nodular surface were found at the site of the kidney. On section they appeared as loose dark red tissue with areas of necrosis and cavities filled with blood. The kidney tissue in places was sharply demarcated from the tumor, but elsewhere it was replaced by the tumor. In three cases the lesion was bilateral. Some of the mice had hemoperitoneum.

Histologically the tumors were variants of angiosarcomas (Fig. 2). Some of them consisted of large cavities, filled with blood, with walls formed by tumor tissue, others had a spongy, honeycombed structure and consisted of anastomosing bands of long or oval cells, the space between which was filled with erythrocytes. Solid regions consisting of round cells with pale cytoplasm and with a small dark nucleus were present. Often there were giant cells with misshapen nuclei. The tumors invaded the kidney tissue, replacing it over wide areas. No metastases could be found.

Pararenal angiosarcoma thus was found to be one of the most frequent tumors caused in males by DMH. In females this carcinogen induces tumors of the anal region, intestine, and uterus but no angiosarcomas of the pararenal cellular tissue were found in the writers' previous experiments in any of 176 female CBA mice receiving DMH according to the scheme described above [2, 3]. Vascular tumors in different situations, including in the pararenal cellular tissue, were found by Toth and Wilson [6] in Swiss mice receiving DMH with their drinking water, but their frequency was the same in males and females. After subcutaneous injection of DMH into Swiss mice, males developed epithelial tumors of the kidneys much more frequently, but never pararenal sarcomas [5].

In the authors' laboratory pararenal angiosarcomas were found in three of five male C3H mice receiving DMH by the same scheme as the CBA mice; there is no information as yet on the appearance of these tumors under the influence of DMH in mice of other lines. There is likewise no information on the mechanisms of the selective appearance of these tumors in male mice; all that can be said is that these tumors did not appear in castrated CBA females.

The development of angiosarcomas of the pararenal cellular tissue under the influence of DMH in male mice is a new and somewhat unusual manifestation of sexual dimorphisms in carcinogenesis, for the tumor concerned is mesenchymal in nature.

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SYNTHESIS OF α-FETOPROTEIN, ALBUMIN, AND TRANSFERRIN BY CONTINUOUS MOUSE HEPATOMA CELLS

Yu. T. Aleksanyan

UDC 616.006-018.1-008.939.6-092.4

The ability of continuous cultures of MGXXIIa mouse hepatoma cells to synthesize α-fetoprotein, albumin, and transferrin was studied by an immunoautoradiographic method. Albumin and transferrin were found in the growth medium of hepatoma cells in the 5th year of culture (55th month), concentrated with polyethylene glycol; no α-fetoprotein could be detected. Only transferrin was found in the growth medium of hepatoma cells in the 8th year of culture (92nd month). Two clonal cultures obtained in the 8th year of culture of hepatoma cells also showed ability to synthesize transferrin. Continuous hepatoma cells preserved their malignancy. In Lyphogel-concentrated sera of mice with tumors formed after inoculation of hepatoma cells in the 5th year of culture, α-fetoprotein was found by the microprecipitation test in agar. No α-fetoprotein was found in the sera of mice with tumors formed after inoculation of hepatoma cells in the 8th year of culture.

KEY WORDS: α-fetoprotein; albumin; transferrin; continuously cultured cells.

The ability of liver tumors to produce α-fetoprotein is utilized for the immunodiagnosis of these tumors [1-3, 9]. Investigation of the synthesis of α-fetoprotein and other serum proteins in cultured hepatoma cells is also of great importance for tagging tumor cells in culture. However, many aspects of this probelm remain unexplained and the literature devoted to its study consists of only isolated communications [5, 7, 8, 10, 11].

The object of this investigation was to study the ability of MGXXIIa mouse hepatoma cells in continuous culture to synthesize α-fetoprotein, albumin, and transferrin.

EXPERIMENTAL METHOD

The MGXXIIa cell line obtained by the writer from a solid form of mouse hepatoma XXIIa [4], and clonal cultures A and B obtained by T. N. Ignatova (Institute of Cytology, Academy

Laboratory of the Molecular Basis of Immunogenesis, Institute of Experimental Biology, Academy of Sciences of the Armenian SSR, Erevan. (Presented by Academician of the Academy of Medical Sciences of the USSR L. M. Shabad.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 88, No. 7, pp. 76-78, July, 1979. Original article submitted August 18, 1978.

0007-4888/79/8807-0759$07.50