VIRUS HEMANGIOMATOSIS OF MICE

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UDC 616-006.311-022.6-092.9

Virus hemangiomatosis transplanted with cellular and cell-free material into CC57BR mice is described. This virus is apparently not identical with the viruses of mouse leukemias, or the virus of Moloney's sarcoma and polyoma.

In experiments undertaken by the writer over a period of more than 15 years, in which mice were inoculated with leukemic material from different sources, the development of multiple hemangiomas in the experimental animals was frequently observed. The tumors were situated mainly in the mesentery and also in the liver and spleen. Hemangiomas produced by polyoma virus have been described in mice and hamsters [1, 2]. However, no separate virus has yet been identified as the causative agent of these neoplasms.

The object of the present investigation was to determine the viral etiologic agent in the tumors which had been observed. The first results of these experiments are described below.

EXPERIMENTAL METHOD

Mice of line CC57BR/Mv, with a low incidence of spontaneous cancer and leukemia, were injected intraperitoneally with saline suspensions (1:3) of cells of hemangiomas discovered in CC57BR/Mv mice and with cell-free twice-centrifuged blood plasma from mice with hemangiomatosis (the plasma was also injected intravenously).

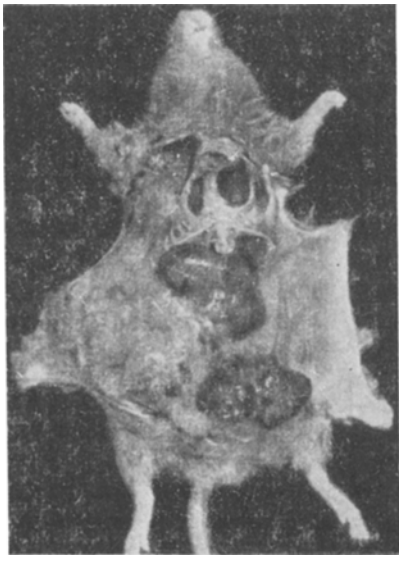

Fig. 1. CC57BR mouse with virus hemangiomatosis (macroscopic appearance).

Simultaneously with the suspension of the tumor or the plasma supernatent, Freund's complete adjuvant (Difco) also was injected.

The diagnosis of the tumors was made on the basis of macroscopic and microscopic studies of the induced tumors.

EXPERIMENTAL RESULTS

Macroscopically detectable neoplasms in the mice had the appearance of multiple (less frequently, solitary) dark red, soft, elastic nodules of different sizes, usually located in the mesentery, in the liver (frequently on the pedicle), and in the spleen (Fig. 1).

Experiments in which these neoplasms were detected are included in Table 1.

The attempt to transplant a hemangioma of the liver, and also a tumor of the mesentery (combined with leukemia)

Laboratory of Experimental Tumor Therapy, P. A. Gertsen Moscow Oncologic Research Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR A. D. Timofeevskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 69, No. 3, pp. 97-100, March, 1970. Original article submitted July 21, 1969.

TABLE 1. Experiments in Which Neoplasms Appeared

Experiment No.	Character of experiment	Line of experimental mice	Time after infection of of mice when tumors first appeared (in months)	Localization and picture of neoplasm
1	Intraperitoneal injection of surviving culture of normal human spleen infected with human leukemic material	CC57BR	19	Nodule on pedicle in liver
2	Injection of a monkey kidney culture, infected with bovine leukemic material, into the spleen	CC57BR	17 22 29 34 (5 mice)	Angiosarcoma of spleen Hemorrhagic cysts Hemangioma of spleen, liver; nodules in mesentery
3	Injection of a human embryonic kidney culture, infected with bovine leukemic tissue, into the spleen	CC57BR	20 (2 mice) 23 (2 mice) 25 (3 mice)	Angioma of liver; nodules in mesentery, in liver, and in spleen
4	Intraperitoneal injection of a primary culture of leukemic mouse spleen	C3HA	24 (2 mice)	Nodules in mesentery and in liver (in first case combined with leukemia)
5	Intraperitoneal injection of supernatant from leukemic mouse tissues	CC57BR	17 19 11	Nodules in mesentery and in liver
6	Offspring of parent mice infected with reticulosarcomatosis virus	CC57BR	21 24 (2 mice)	Nodule on pedicle in liver; nodules in mesentery
7	Parents of young mice infected with reticulosarcomatosis virus	CC57BR	24	Nodule in mesentery
8	Mice vaccinated against reticulosarcomatosis	CC57BR	10	Nodule in mesentery
9	Uninfected human embryonic kidney culture	CC57BR	17 28 36	Hemangiomas of liver, spleen, nodules in mesentery

did not yield definite results. It is interesting to note that in one case of transplantation of leukemia into CC57BR mice, one of the mice (although not developing leukemia) developed a hemangioma of the liver 4 months after transplantation.

Successful transplantation was achieved from a mouse with hemangioma of the liver from experiment 2 (Table 1). In the first two cases hemangiomatosis appeared 7 months after intraperitoneal injection of a suspension of liver hemangioma. In one case a CC57BR mouse was inoculated simultaneously with cellular material and Freund's adjuvant, while in the other case no adjuvant was given. In the case of transplantation of the hemangioma together with injection of adjuvant, hemangiomas began to appear in the inoculated mice after 50 days (with an angiosacroma in one case), and the tumors were located in the mesentery. In the second case the tumors appeared much later. Inoculation with cellular and cell-free (blood plasma, centrifuged twice and not containing whole cells) material from these tumors led to the development of hemangiomatosis after a mean latent period of two months.

The first analysis to differentiate between hemangiomatosis virus and other oncogenic viruses yielded the following results: 1) intramuscular injection of cell-free extract of a hemangioma into BALB/c mice aged 4-6 days did not cause the appearance after one month of rhabdomyosarcomas characteristic of Moloney's sarcoma virus: 2) titration of mouse serum for the presence of antibodies against polyoma virus in the delay of hemagglutination test revealed "background" antibodies in dilutions of 1:400-1:800 (I. Irlin). It must also be remembered that CC57BR mice are naturally highly resistant to polyoma virus. Electron microscopy of tumor sections revealed virus particles measuring about 80 mμ (I. Glezer).

The virus etiology of hemangiomatosis (angiosarcoma) of CC57BR mice was thus established. The strain of the new virus is maintained by passage through mice.

Preliminary analysis shows that hemangiomatosis virus is not identical with the viruses of mouse leukemias or with the virus of Moloney's sarcoma and polyoma virus. The pathomorphology of hemangiomatosis and the possible connection between this neoplasm and leukemias, and its biological properties will be examined in the next communication.

LITERATURE CITED

1. V. Defendi and J. M. Lehman, Cancer Res., 24, 329 (1964).
2. S. E. Stewart et al., J. Nat. Cancer Inst., 20, 1223 (1958).