SOME PROPERTIES OF METASTASIZATION OF INDUCED TUMORS AND THEIR PASSAGES IN RATS

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The study of the principles governing the metastasization of malignant neoplasms is of great importance in experimental and clinical oncology, for it gives a deeper insight into the biological nature of malignant growth. We know that metastasization has been studied mainly in connection with transplanted tumors [2-8, 10-14]. However, it may be considered that the metastasization of transplanted tumors does not fully reflect the true nature of this process. This may be explained by the fact that the tumors undergo considerable modification in an immunobiological respect during passage [1,9,15].

For these reasons, it is of definite interest to study the principles governing the metastasization of induced (primary) tumors, for these more closely resemble spontaneous tumors.

In the present investigation, some of the principles of metastasization of induced tumors and of the same tumors after passage in rats were studied.

EXPERIMENTAL METHOD

Experiments were carried out on 768 rats of the Wistar line of both sexes, aged 1-18 months. One hundred of these rats at the age of 8 months received an injection of 9,10-dimethyl-1,2-benzanthracene (DMBA) in a dose of 5 mg, dissolved in mineral oil. The carcinogen was injected into 50 female rats into the muscle tissue of the left hind limb, and into 50 male rats into the right testis. The injection of the carcinogen into different parts of the body was determined by the fact that it was intended to compare the character of metastasization of tumors induced in muscle tissue and in the testis with the metastasization of transplanted tumors grafted into the same parts of the body. For this purpose, induced tumors and their subsequent 12 passages in rats of the same line were taken. Since it has been shown [6,11] that primary tumors metastasize best when transplanted into the spleen, it was decided to find out how metastasization of tumors subjected to passage would take place when these were transplanted into this organ.

A 5% suspension of tumor tissue in physiological saline was injected into the rats in doses of 1 ml (subcutaneously),0.5 ml (into the testis), and 0.2 ml (into the spleen). The development and localization of the metastases were investigated in rats dying from tumors or on the verge of death, by counting the regions on the surface of the organ and then in sections 5 mm in thickness. The morphological structure of the primary tumors and of their metastases was studied in ordinary histological sections stained with hematoxylin-eosin.

EXPERIMENTAL RESULTS

In all 50 female rats receiving DMBA, tumors developed with a latent period of growth of 2.5-3 months. The tumors were of different sizes, and at the time of death of the animals (4.5-6 months) their mean dimensions were 6 × 8 × 8 cm and they weighed from 100 to 190 g. In their histological structure, they were rhabdomyosarcomas

Metastasization of Induced Tumors and Tumors Subjected to Passage in Rats

Organ and tissue	Induced by DMBA		Passage of induced polymorphocellular rhabdomyosarcomas																			
			1st			2nd			3rd			5th			8th			12th				
			Metastasization after transplantation																			
	Muscle	Testis	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen	Subcutaneously	Into testis	Into spleen
Lungs	+	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Liver	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Kidneys	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Stomach	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Intestine	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Mesentery	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+
Diaphragm	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+
Omentum	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+
Peritoneum	-	+	-	-	+	-	-	+	-	-	+	-	+	+	-	+	+	-	+	+	-	+	+
Abdominal lymph glands	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+
Perirenal cellular tissue	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+	-	+	+

Note: + development of metastases; – negative results.

and fibrosarcomas*. In one case, the tumor was a polymorphocellular sarcoma with areas of mammary gland adenoma.

The tumors induced in the region of the left hind limb metastasized in the lung in 28 rats (54%), in the abdominal lymph glands in 14 cases (28%), in the diaphragm in 9 cases (18%), in the perirenal cellular tissue in 2 cases, and in the omentum and mesentery in 2 cases. The same tumors, after passages in rats, when transplanted into the region of the left hind limb never metastasized in the internal organs at any passage. As a rule, the rats died in this case between the 18th and 20th days (mean 24.8 days). However, when the tumors grew for a long time (40-70 days, mean 43.3 days), metastasization was observed in the regional lymph glands.

Of the 50 male rats taken in the experiment, only 3 developed tumors in the testis after 7-8 months, and these in their histological structure were polymorphocellular sarcomas. The tumors induced in the testis metastasized in the lungs, liver, kidneys, mesentery, omentum, abdominal lymph glands, and perirenal cellular tissue. Small tumor nodules were found on the surface of the intestine and stomach, in the spleen, and on the peritoneum. The same tumors, after passages in rats, when transplanted into the testis at the first passage, produced single metastases in the diaphragm, omentum, abdominal lymph glands, and perirenal cellular tissue. In this case, no metastases were found in the internal organs. After the third passage, more intensive metastasization of the tumors transplanted into the testis was observed. For instance, in the first two passages, no metastases were found in the peritoneum and mesentery, while in subsequent passages, the tumor metastasized in these tissues, and conglomerates of tumor tissue were found in the omentum and the abdominal lymph glands. In this case, the rats died from the tumor between the 17th and 28th days. Tumors induced in the testis and muscle, when transplanted into the spleen, metastasized equally, starting from the first passage. Metastasization took place intensively in the liver, diaphragm, omentum, mesentery, abdominal lymph glands, peritoneum, perirenal cellular tissue, stomach, and intestine. After transplantation of the tumor into the spleen and testis, the rats frequently developed ascites, the fluid containing blood cells and individual cells of atypical form.

The results describing metastasization of the induced tumors and their passages are summarized in the table. Since the tumors from the third to the twelfth passage metastasized in the same parts of the body, the results of metastasization are given in the table for the 1st, 2nd, 3rd, 5th, 8th, and 12th passages.

*Reported by corresponding member AMN SSSR, A. A. Solov'ev.

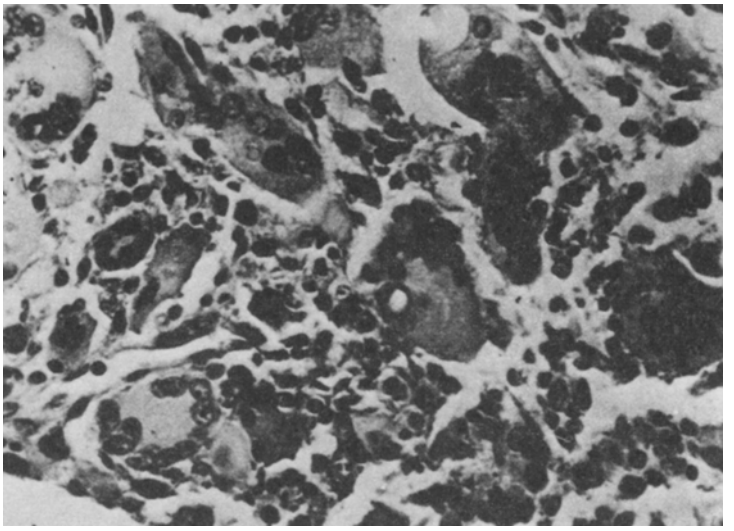

Fig. 1. Tumor induced in testis, with giant multinuclear cells. Hematoxylin-eosin 200×.

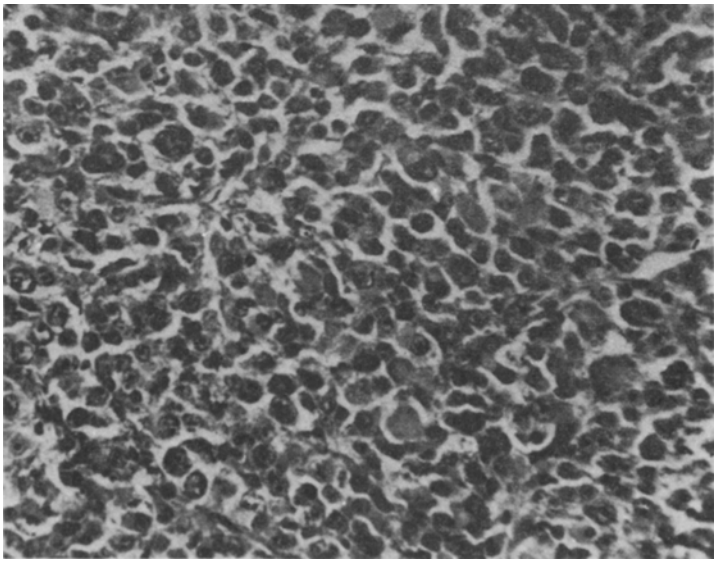

Fig. 2. Metastases of a tumor induced in the testis. No giant cells present. Hematoxylin-eosin 200×.

The results show that metastasization of induced tumors in the muscle and testis differs from metastasization of their passages transplanted into the same places. These tumors, transplanted into the spleen, starting from the first passage, metastasized equally in all passages investigated. The histological structure of the primary induced was basically the same as the structure of their metastases. However, cases were observed in which the primary tumors contained giant cells with several nuclei (Fig. 1), while their metastases did not contain these cells (Fig. 2). Evidently, this may be explained by cell selection taking place during metastasization.

Hence, the results indicating differences in the metastasization of induced tumors and their passages must be taken into consideration during the study of the principles governing the metastasization of malignant neoplasms.

LITERATURE CITED

1. C. Dukes, Proceedings of the VIIIth International Cancer Congress, Vol. 3 [in Russian], Moscow (1963), p. 230.
2. T. P. Evgen'eva, Byull. éksp. biol., 5, 76 (1964).
3. N. S. Kiseleva and U. Min, Vopr. onkol., 1, 27 (1960).
4. N. A. Krotkina and A. M. Troitskaya, in the book: Problems in Oncology, No. 1 [in Russian], Moscow (1949), p. 146.
5. M. S. Lomakin, Vopr. onkol., 4, 39 (1961).
6. M. S. Lomakin and Yu. S. Krivoshein, Byull. éksp. biol., 11, 7 (1965).
7. I. N. Maiskii, M. S. Lomakin, and P. P. Filatov, Vestn. AMN SSSR, 2, 22 (1959).
8. A. A. Solov'ev, Arkh. biol. nauk SSSR, 45, 2, 139 (1937).
9. J. Colter, H. Bird, H. Koprowski, et al., Nature, 177, 993 (1956).
10. W. Dunning et al., Cancer Res., 5, 256 (1946).
11. F. Endler, Zt. Krebsforsch., 15, 339 (1916).
12. E. Hlavayova and P. Kossey, Csl. Onkol, 2, 133 (1955).
13. T. Joshida, Un. int Cancr., Acta, 16, 496 (1960).
14. W. Krischke, Acta biol. med. germ., 3, 2 (1959).
15. L. Law, Proc. Am. Ass. Cancer. Res., 2, 129 (1956).

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
