MORPHOLOGICAL CHANGES IN MAMMARY GLAND CANCER OF RATS (RMK-1) UNDER CONDITIONS OF REPEATED TRANSPLANTS

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It is known that as early as in the first generations, and sometimes also in established strains obtained through transplantation of spontaneous tumors, marked changes are observed in the biological properties of the tumor, directed toward an increase in malignancy. This process may be accompanied by changes in the morphology of the transplanted tumors [6, 8, 9].

In the opinion of the majority of authors, the morphological changes of the tumors in the process of serial transplantations results in a decrease in the differentiation of the tumor, which is manifested, above all, by a loss of the ability to form specific structures [1, 2, 10]. These changes have been studied primarily in material from mice [7, 11]. At the same time, mammary gland cancer of rats is a more perspective experimental model, since its reactivity, in the process of hormonotherapy, is close to that seen in man [4, 12].

In 1958, we obtained a transplantable rat mammary gland cancer (RMK-1), possessing, in the first generations, a manifest reactivity to hormones [4], and, according to its morphological structure, presenting as a characteristic rat alveolar carcinoma [3]. By 1961, RMK-1 had already been passed through more than 30 generations, in the process of which we observed changes in the reactivity of this tumor to hormonal action [5] and changes in its morphological structure.

In this work, we provide a description of the morphological changes that occurred in the tumor in the course of 32 generations.

The original tumor, and the tumors of the first generations (2nd, 4th, 7th) consisted of rather coarse alveoli, filled with poorly differentiated cells. The epithelium of the alveoli possessed a manifest tendency toward the formation of adenomatous (pseudoglandular) structures (Fig. 1). There was little secretion in the tumor. Occasionally, we observed areas of adenomatous structure, in which the alveoli were filled with secretion, but the epithelial lining consisted of only 1-2 layers of cells. The secretion was principally dense and homogeneous, with a small number of large vacuoles, and it stained well with eosin. There was minimal desquamation and cornification of the epithelial cells. The tumor cells were small, dark, possessed little chromatin, and contained poorly visible nucleoli. We noted a very small number of mitoses. The stroma of the tumor consisted of small rods of loose connective tissue.

By the 10th generation, the structure of RMK-1 had already been altered considerably. Above all, the dimensions of the alveoli were sharply increased. Occasionally, gigantic cells were noted, visible macroscopically. A large central cavity appeared in the alveoli, and the epithelium was arranged in the wall of the alveolus in the form of a wide layer, inside which we observed a large number of pseudoglandular cavities of varying size and form. The amount of secretion in the tumor decreased sharply, and its morphology was clearly altered: it was principally reticular in character, and stained weakly with eosin. In the central cavity of the alveolus, in addition to secretion, there appeared a large number of shadow cells and large amounts of cellular detritus. Accoding to morphology, the tumor cells remained almost the same as the cells of the first generations. They were small, dark, with a narrow ring of protoplasm and a more compact nucleus of intermediate size. The nucleolus was observed only in individual cells. Mitoses were encountered rarely. The stroma of the tumor did not change, and, as before, consisted of rods of loose connective tissue.

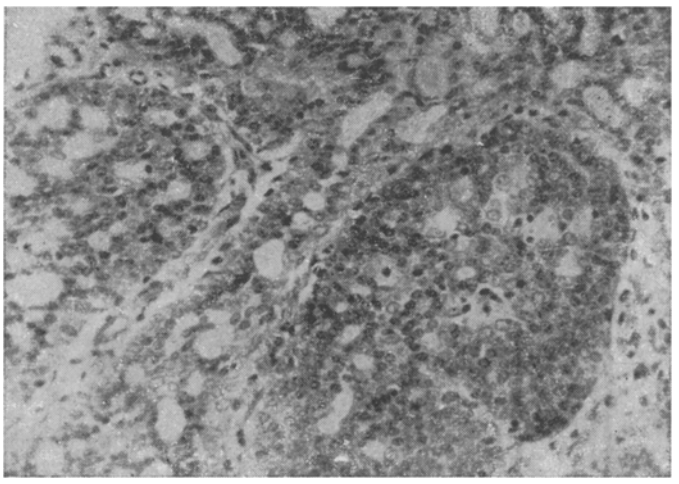

Fig. 1. Structure of a tumor of the 1st generation of transplantable rat mammary gland carcinoma (RMK-1). The adenomatous structure of the tumor is well visualized. Stained with hematoxylin-eosin. Magnification 270×.

By the 18th generation, the structure of the tumor markedly differed from that observed in the 1st generation. The dimensions of the alveoli increased even more. A central cavity was clearly seen in almost all the alveoli, inside which one observed cornified cells and granular masses of cellular detritus, which stained well with eosin. Secretion became still more minimal, and in the cavity of the alveoli and the pseudo-glandular structures it had the form of weakly basophilic threads. Characteristic of this generation was the appearance of areas of growth of fibroblast-like epithelial cells, superficially resembling the growth of connective tissue cells in tissue culture. The dimensions of the cells increased somewhat, mainly due to an increase in the size of the nucleus. The number of mitoses in the tumor increased significantly.

In the 32nd generation, the general structure of RMK-1 differed little from that described in the 18th generation. However, in contrast to the latter, the zones of fibroblast-like epithelium adjoining the central cavity of the alveoli were apparent in almost all the alveoli, resulting in the loss of the adenomatous structure of the tumor (Fig. 2a). Along with this, a large number of small alveoli were formed in them, with a solid type of structure. There was almost no secretion at all in the tumor. It appeared as isolated, very thin, weakly basophilic threads, and the cavities of the alveoli were filled primarily with cellular detritus. In this generation, we also observed significant cytological changes. The dimensions of the cells increased markedly, mainly due to an increase in the size of the nuclei. In the zone of fibroblast-like epithelium the nuclei of the cells were intensely elongated. In the larger and lighter nuclei of the epithelial layer the structure of the chromatin network became more clearly defined, and, as a rule, the nucleolus was readily apparent (see Fig. 1; Fig. 2b). Mitoses in the tumor were numerous (2-4 per visual field under high magnification). The stroma remained unchanged.

Thus, in the process of serial transplantation there occurs a progressive decrease in differentiation of the tumor: secretion diminishes, and there is a reduction in the ability to form glandular structures. One also notes certain cytological signs of tumor dedifferentiation: the size of the nucleus increases, the structure of the chromatin network becomes more clearly defined, and the nucleolus becomes more evident. At the same time, changes arise that are characteristic of an increase in the malignancy of the tumor: the number of mitoses increases, and there appears areas of solid epithelial growth and growth zones of atypical, fibroblast-like epithelium.

It must be emphasized that in parallel with the morphological dedifferentiation of the tumor, there also occurs a progressive reduction in its reactivity to hormonal action, down to the appearance of area activity [5].

From the data obtained, it would follow that by approximately the 10th generation the use of transplantable rat mammary gland cancers is not expeditious for purposes of experimental hormonotherapy.

SUMMARY

During the process of consecutive inoculations of rat alveolar milkduct carcinoma (RMC-1) – from the 2nd to the 32nd generations the authors observed considerable morphological changes, manifested by the reduction of tumor

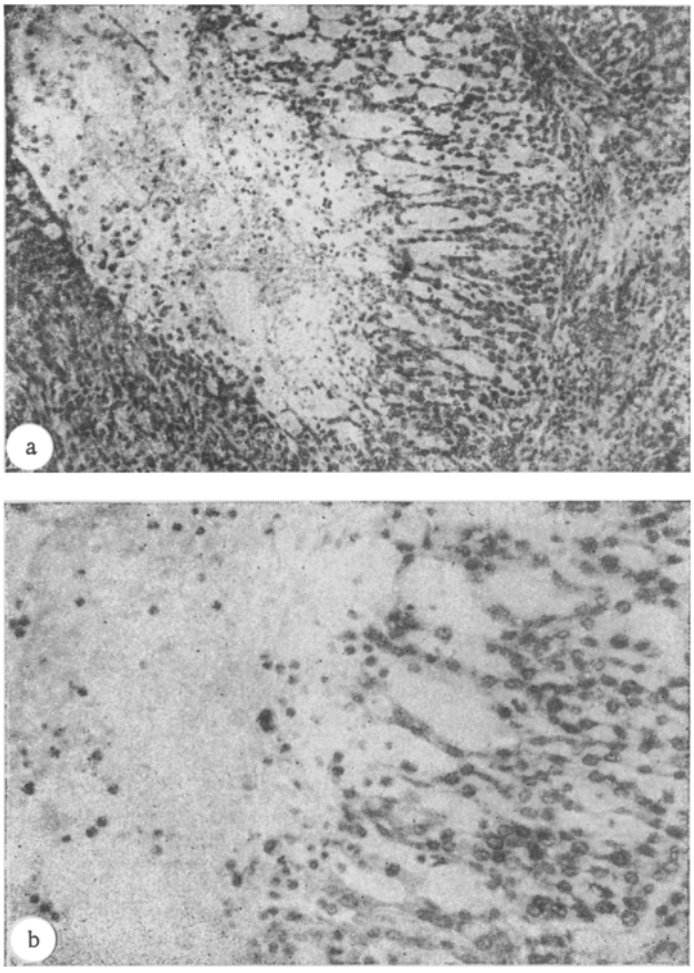

Fig. 2. Structure of the tumor in the 32nd generation of RMK-1. a) At magnification of 130×. The adenomatous character of the tumor is lost; b) at magnification of 270×. The atypical fibroblast-like epithelium is visible. Tendency toward the formation of adenomatous structures is manifested weakly. The dimensions of the nuclei are enlarged. Stained with hematoxylin-eosin.

differentiation (diminished secretion and decreased capacity to glandular structure formation) and by some cytological signs of dedifferentiation (enlargement of the nucleus, a more distinct chromatin network structure, and separation of the nucleolus). Besides, there appeared areas of solid epithelial growth and strata of atypical fibroblast-like epithelium. The number of mitoses also increased, pointing to an intensification of tumor malignancy.

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