A Syndrome of Multiple Telangiectases Produced by a Transplantable Fibrosarcoma

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With the “granuloma-pouch” technic, it was possible to induce metastasizing and transplantable fibrosarcomas by the chronic topical application of concentrated croton oil solutions in the subcutaneous tissue of the rat (9). Two of these neoplasms—designated, respectively, as “croton-pouch tumor” No. 1 and No. 2—have been maintained in this Institute by serial transplantations in Sprague-Dawley rats for almost 2 years, because they proved to be useful in the study of various problems related to neoplastic growth (6, 8). Originally, these tumors were rather polymorph in their histologic appearance and contained islets of chondrosarcomatous and osteosarcomatous tissue; but gradually they have assumed a purely fibrosarcomatous aspect after many transplantations, and now the two tumors are strikingly similar in their histologic structure, except that tumor No. 1 is somewhat more fibrous (Fig. 1). Macroscopically, tumor No. 1 distinguishes itself from the other only in that it is harder and grows much more slowly than No. 2. Since only tumor No. 2 takes in virtually 100 per cent of the cases when injected in the form of a cell suspension, it has become customary to transplant tumor No. 1 in the form of slices. Even so, this neoplasm does not take invariably.

A curious systemic syndrome develops in the bearers of croton-pouch tumor No. 1 when the sarcomas become very large, usually between the 25th and the 60th day after grafting. This communication describes the histologic characteristics of this syndrome and considers its relationship to the implanted tumor.

MATERIALS AND METHODS

Female Sprague-Dawley rats, with an average initial body weight of 160 gm. (range: 150–180 gm.) were used. The animals were kept exclusively on Purina Fox Chow and tap water.

Transplantations were performed under sterile conditions as follows: The shaved rat was anesthetized with ether, and a small (1.5-cm.) transverse incision was made through the skin in the lumbar region. Then a closed forceps was introduced under the skin, up to the neck of the rat, and slightly opened in this position, so as to prepare a channel for the graft in the subcutaneous tissue. A disc of tumor tissue (about 1.5 cm. in diameter and 3 mm. in thickness) was introduced through the connective tissue channel and deposited in the upper thoracic region, underneath the skin. Finally, to prevent the graft from slipping back toward the incision, a stitch was placed through the skin and the fascial layers, about 1 cm. below the graft; the skin incision was then closed with two additional stitches. On the 4th day after the grafting, all three stitches could be removed.

The animals died or were killed with chloroform between the 20th and 57th days after grafting, and their tissues were fixed in Susa solution for subsequent weighing and histologic study. Paraffin-embedded sections were stained with hematoxylin-eosin and also according to the Hotchkiss-McManus technic (5), to detect PAS-positive (periodic acid-Schiff) granules and mast cells.

RESULTS

There was little or no relationship between the duration of the experiment and the systemic changes. The organ lesions were roughly proportional, on the other hand, to the size of the tumors in a series of more than 500 transplantations. We have therefore selected, at random, one experiment on 41 rats for special study, listing separately in Table 1 the mean values (with their standard errors) in Group I, in which the tumors had failed to take (or involuted); Group II, in which the tumors were comparatively small (18–48 gm.); and Group III, in which the tumors were comparatively large (57–220 gm.). Perusal of the table shows that the weights of the adrenals, kidneys,
and spleens were in fact roughly proportional to the size of the tumors. For the ovaries this relationship was not clear, and the body weight (exclusive of the neoplasms) remained curiously unaffected by these large and often fatal tumors.

Since, qualitatively, the morphologic changes in the various organs were essentially the same in all animals, we can discuss them here conjointly.

The most constant and striking lesions occurred in the adrenals. Even gross inspection revealed a pronounced hypertrophy of the gland with a peculiar mottled reddish discoloration of its surface. Histologic examination showed that the enlargement was due primarily to an enormous dilatation of the cortical sinusoids, so that in many cases the gland looked like a cavernous body. The connective tissue stroma, especially the capsular connective tissue, was also greatly increased. These changes disorganized the normal structure or the cortex to such an extent that, usually, the columnar arrangement of the fasciculata was no longer recognizable. Within the capsule, there was often a well defined layer of epithelioid elements, containing numerous PAS-positive cell inclusions. Such granules were also seen in the glomerulosa cells just underneath the capsule and, more rarely, in other parenchymatous elements of the deeper cortical layers. The endothelial cells of the cortical sinusoids were hypertrophic, their nuclei protruding deeply into the lumen, and in many cases large numbers of round cells (presumably desquamated from the endothelium) were seen in the cortical capillaries.

The size of the adrenal medulla was much less markedly affected, and the vessels in this part of the gland never exhibited the intense cavernomatous dilatation so characteristic of the cortical sinusoids. Yet the structure of the medulla was also greatly disorganized, mainly owing to a proliferation and edematous imbibition of the connective tissue. The chromaffin cells tended to be smaller than normal, perhaps owing to compression by the proliferating stroma (Figs. 2–7).

Very similar changes were seen in the ovaries. Here the telangiectatic dilatation of the vessels was most pronounced in the corpora lutea, some of which were transformed into actual pools of blood. We never saw tumor metastases or thrombi anywhere in the vascular lumina, and the blood within the dilated vessels was always of normal appearance, so that the telangiectases could not be ascribed to stasis resulting from vascular occlusions. PAS-positive granules were not seen in the corpus luteum cells, but proliferation of endothelia was often just as evident here as in the adrenal cortex. The follicles showed no conspicuous changes, but the stroma was often edematous, and sometimes it contained an unusually large number of mastocytes (Figs. 8–11).

The kidneys looked quite abnormal, even upon mere macroscopic inspection, in that they usually exhibited a peculiar greenish discoloration with numerous fine, dustlike, red spots. Upon histologic examination we were unable to detect any pigment granules, but the tubules—especially in the outer cortex—were usually filled with large, slightly PAS-positive, eosinophilic colloid droplets, which may have accounted for the singular diffuse discoloration of the organ. The dustlike red spots, on the other hand, undoubtedly corresponded to the telangiectatic glomerular capillaries throughout the renal cortex, which were perhaps the most striking histologic changes in this organ. Here again we were unable to find any vascular obstruction to account for the dilatation, which was usually limited to the individual glomerular loops (Figs. 12–15).

The enlargement of the spleen proved to be due mainly to a proliferation of lymphopoietic and myelopoietic elements, with a considerable increase in the number of splenic megakaryocytes. The sinusoids of the spleen also contained a large number of free, hemopoietic cells.

The parenchymatous cells of the liver were not characteristically affected, but the sinusoids were often dilated, though never to the extent of forming true telangiectases such as were noted in the adrenal cortex, the ovary, and the kidney. The
reticulo-endothelial Kupffer cells lining the hepatic sinusoids were hypertrophic, and many apparently detached endothelial elements were seen free in the lumina of the sinusoids.

The sinusoids in the bone marrow were likewise dilated and particularly rich in free hemopoietic elements; in this respect they resembled the sinusoids of the spleen.

On the other hand, no capillary dilatation or proliferation of endothelia was observed in the heart, bone tissue, muscle, subcutaneous connective tissue, or the excretory tissue of the pancreas. Even in the islets of Langerhans (whose sinusoids resemble those of the renal corpuscles and the corpora lutea), telangiectases were never seen. The thymus revealed a mild degree of atrophy, undoubtedly due to the stressor action of the large tumors. The anterior lobe of the pituitary was undoubtedly due to the stressor action of the large tumors. The anterior lobe of the pituitary was
dilated and particularly rich in free hemopoietic elements; in this respect they resembled the sinusoids of the spleen.

Finally, it should be pointed out that, in every rat with the telangiectatic syndrome, the heart was enormously dilated (though not hypertrophied) and the blood volume was manifestly increased, as judged by the enormous amount of blood that could be collected on sponges after sectioning of the vena cava.

DISCUSSION

We appear to be dealing with a syndrome characterized by the extreme dilatation of the smallest capillary and sinusoid vessels, especially in the adrenal cortex, the corpora lutea, the renal glomeruli, and the bone marrow. No such telangiectatic changes were observed in any of the other organs which we examined. At the same time, there was a marked hypertrophy and desquamation of endothelial cells in the organs in which telangiectases had developed, as well as some increased myelopoiesis with megakaryocyte formation in the spleen. The intensity of these systemic changes was proportional to the size of the tumor, and the syndrome was invariably absent in ani-

mals in which the tumors had involuted. It is most probable, therefore, that the syndrome is a consequence of the tumor, but the mechanism through which this neoplasm produces such systemic manifestations and the significance of the latter remain to be established.

In our Institute, many thousands of transplantations have been performed during the last few years under exactly comparable conditions, with the Walker tumor, the Novikoff hepatoma, the Murphy rat lymphosarcoma, etc., yet a similar syndrome has never been observed in rats bearing neoplasms other than the croton-pouch tumor No. 1. Even the closely related croton-pouch tumor No. 2—which histologically resembles No. 1 and was induced in a similar manner—has never been observed to produce the multiple telangiectatic syndrome.

In our experience the only change that bears some remote resemblance to the syndrome described here is that induced by very large Walker tumors. It will be recalled that these also produce rather specific changes in the adrenal cortex, with a proliferation of reticulo-endothelial cells and a marked splenic enlargement. However, histologic studies of the organs affected by Walker tumors reveal only marked ectopic myelopoiesis (especially in the adrenal cortex, the spleen, the liver, and the renal pelvis), but no telangiectases. The literature concerning the systemic manifestations of Walker tumors has recently been reviewed elsewhere (7), so that we need not discuss it further here.

On the other hand, the telangiectatic syndrome is strikingly similar to the systemic lesions which had been produced by certain transplanted granulosa-cell tumors in mice. Here extreme dilatation of minute blood vessels has been observed in essentially the same organs in which we noted them after implantation with the croton-pouch sarcoma (1, 2, 10). If mice bearing granulosa-cell tumors are united in parabiosis with control litter-mates, the hypervolemia and the telangiectases develop only in the tumor-bearing parabiont. From this

FIG. 1.—Histologic appearance of a typical "croton-pouch tumor No. 1." The neoplastic cells are rather regularly arranged around greatly dilated thin-walled vessels. This and all following sections were stained with the PAS-technic. ×100.

FIG. 2.—General view of the cortex in a control rat of Group I, in which the tumor failed to take. Note essentially normal structure of the three layers and of the adjacent medulla. ×40.

FIG. 3.—Corresponding region from a tumor-bearing rat. The capsule is thickened and contains dark PAS-positive epithelioid cells intermixed within the connective tissue. Large telangiectatic spaces are seen, especially in the subcapsular and reticularis layers, but not in the medulla. This and all subsequent photographs (except the controls, Figs. 8 and 12) illustrate sections taken from rats of Group III, which bore particularly large growths of "croton-pouch tumor No. 1." ×40.

FIG. 4.—High magnification of a region from the capsule of the adrenal shown in Figure 3. Note polyhedral epithelial cells with numerous PAS-positive (here black) droplets within the capsular connective tissue. ×420.

FIG. 5.—Outer region of the cortex from another tumor-bearing rat. Here the rather selective telangiectatic transformation of the glomerulosa sinusoids is particularly evident. The fasciculata is much less hyperemic, but the typical columnar arrangement of its cells is lost. ×100.
FIG. 6.—Higher magnification of the disorganized fascicula-ta of the rat shown in Figure 3. ×250.

FIG. 7.—Higher magnification of the reticularis of the rat shown in Figure 3. The sinusoids are so much dilated that the epithelial cells appear compressed between them. The adjacent medulla (right side of field), on the other hand, has a particularly dense structure, without telangiectases. ×100.

FIG. 8.—Normal corpus luteum from a control rat of Group I. ×50.

FIG. 9.—Beginning telangiectatic transformation of the vessels in the corpus luteum of a tumor-bearing rat. The arrangement of the parenchymatous cells is disorganized and resembles that of the reticularis in the adrenals. ×50.

FIG. 10.—Particularly pronounced cavernous dilatation of the blood vessels in a corpus luteum. At first sight, the cavity gives the impression of being a cystic follicle, but actually it is filled with circulating blood and partially subdivided by septa which represent the stroma of this cavernous body. Under high magnification, typical corpus luteum cells could be identified in the wall of this body. ×50.

FIG. 11.—High magnification of the edematous stroma in the medulla of the same ovary. Note that the interstitial cells are very atrophic and the vessels dilated. ×100.
Fig. 12.—Normal glomerulus and convoluted tubules (most of them proximal) in the renal cortex of a control rat from Group I. X450.

Fig. 13.—Telangiectatic dilatation of several individual capillary loops within a glomerulus of a tumor-bearing rat. Note also occasional PAS-positive droplets within the surrounding proximal convoluted tubules. X450.

Fig. 14.—Glomerulus, in which a single capillary loop is enormously dilated. X450.

Fig. 15.—Diffuse but moderate dilatation of glomerular capillaries and intense “colloid degeneration” of the surrounding proximal convoluted tubules, which are loaded with PAS-positive hyalin bodies of various sizes. Note that, in the telangiectatic capillaries of the glomeruli (Figs. 13–15), as in those of the adrenal cortex (Figs. 5–7) and corpus luteum (Figs. 9, 10), the blood cells are normal and there is no indication of thrombosis. X450.
observation it had been concluded that the syndrome is unlikely to be caused by an infectious agent (12); yet it is noteworthy that the estrogenic action of the tumor likewise affected only the tumor-bearing twin. In view of this, it is difficult to exclude the possibility that an infectious agent (e.g., a virus) was responsible for the syndrome but caused sufficiently massive infection only in the tumor-bearing. Perhaps—like the estrogens—the causative agent did not traverse the parabiotic barrier freely.

Essentially similar hypervolemia with telangiectases has been noted in mice with Leydig-cell tumor grafts (19), while a transplantable luteoma caused polycythemia in the mouse (4).

Excessive ectopic proliferation of bone marrow tissue with many megakaryocytes occurs in various locations—most commonly in the spleen and adrenals—both with the "myeloid metaplasia syndrome" (induced by Walker tumors) and with the "hypervolemia syndrome" (elicited by grafts of granulosa tumors, Leydig-cell tumors or croton-pouch tumor No. 1). The possibility must therefore be considered that there is some close pathogenetic relationship between these systemic manifestations of tumor grafts, but the nature of the causative agent remains obscure.

In mice which responded with the hypervolemia syndrome to granulosa-cell tumor grafts, no such changes were elicited by a variety of other non-endocrine neoplasms. The possibility had to be considered, therefore, that the systemic manifestations are due to a steroid hormone, to a hormonally inactive steroid metabolite, or to some other specific hormonal product of neoplastic endocrine cells (3). The croton-pouch tumor No. 1, however, was induced in the subcutaneous connective tissue of the rat; it exhibited the histologic characteristics of a spindle-cell sarcoma, and we have no evidence that this neoplasm can produce any known hormone. Besides, although this telangiectatic syndrome has never been observed previously in the rat, it has recently been noted in mice bearing transplants of parotid tumors (11), which contain no typical endocrine cells. Nevertheless, the ability to produce this syndrome must be rather specific, because we have never observed it among many hundreds of rats which we have transplanted with the closely related "croton-pouch tumor No. 2." It remains to be seen whether our "croton-pouch tumor No. 1" elicits its systemic effects through the production of some humoral substance which—like acetylcholine, histamine, or serotonin—can be liberated from structures not possessing the morphologic features of typical endocrine cells.

Experiments designed to extract the factor responsible for the systemic manifestations of croton-pouch tumor No. 1 are now under way.

SUMMARY

Rats bearing grafts of "croton-pouch tumor No. 1" develop singular and rather specific systemic changes, about 4 weeks after grafting, when the neoplasms become comparatively large. This syndrome consists in the formation of telangiectases, with pronounced proliferation of endothelial cells in the adrenal cortex, the corpora lutea, the renal glomeruli, and the bone-marrow. At the same time, there is splenic enlargement with a marked increase in the number of myelopoietic elements and megakaryocytes in the spleen. The morphologic characteristics of this syndrome have been described in detail and illustrated by microphotographs, but it was not possible to clarify its pathogenesis or functional significance.

REFERENCES

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