Metastasis in a Transplantable Mammotrophic Pituitary Tumor

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SUMMARY

Two strains of a mammatrophic pituitary tumor were compared; the secretion of adrenocorticotropic hormone had declined appreciably in one and, in the other, was unchanged. The secretion of adrenocorticotropic hormone by the pituitary tumor does not appear to be related to the capacity for metastasis inasmuch as metastasis was observed in the retroperitoneal lymph nodes of animals bearing both types of tumor. The microscopic picture as well as ultrastructure of the metastases were identical to that of the primary tumor. Metastases were not observed grossly or microscopically in any other organs. The size of the altered tumor was considerably larger than that of the unchanged one. The adrenal glands were significantly smaller in animals bearing the altered tumor, compared with those from animals bearing the unchanged tumor.

INTRODUCTION

The MtT-F4 mammatrophic pituitary tumor developed by Furth secretes tremendously elevated quantities of ACTH, growth hormone, and prolactin (2, 5). The tumor was first induced by injection of the synthetic estrogen, diethylstilbestrol (8, 9). In the 1st generations, the tumor was estrogen dependent, but after several generations, it became autonomous. Splanchnomegaly is attributable to the hormones secreted by the tumor (10). The adrenal glands are stimulated by the ACTH in conjunction with growth hormone and prolactin, and adrenal weight is increased to more than 10 times that of controls (3, 10). Mammary glands also become hyperfunctional. After numerous passages, we have observed that the tumor loses some of its capacity to secrete the ACTH. In this report, we have observed metastasis to the retroperitoneal lymph nodes in a strain of the MtT-F4 tumor exhibiting reduced ACTH secretion as well as one with elevated ACTH output.

MATERIALS AND METHODS

The MtT-F4 tumor was obtained from Dr. Robert Bates, Endocrine Research Laboratory, National Institutes of Arthritis and Metabolic Diseases. After 10 passages, ACTH secretion was decreased, as indicated by reduced adrenal weight, compared with that observed previously in our laboratory. In spite of the reduced ACTH secretion, the tumor was maintained in our laboratory. New tumor was then obtained from Dr. Bates who has been able to regrow the tumor after freezing some of the initially very actively secreting strain. Forty-five female Fischer F344 rats were obtained from Microbiological Associates, Inc., Walkersville, Md. Fifteen rats received injections of altered tumor in the lateral aspect of the thigh (Group 1), whereas another 15 rats (Group 2) received the newly acquired tumor. The remainder of the rats served as non-tumor-bearing control animals (Group 3).

All animals were sacrificed after 6 weeks. After decapitation, the adrenals were weighed fresh, and the organs were placed in formalin before being trimmed and weighed. Retroperitoneal lymph nodes as well as a small piece of grossly nonnecrotic tumor were fixed for electron microscopy in 3% glutaraldehyde (Ladd Research Industries, Burlington, Vt.) buffered to pH 7.3 with 0.1 m phosphate. Tissues were rinsed in ice-cold 0.1 m phosphate (pH 7.3) and processed according to the procedure reported previously (11). Thin sections were cut on a Porter-Blum MT-1 ultramicrotome (Ivan Sorvall, Inc., Newtown, Conn.) and stained with uranyl acetate (17) and lead citrate (14) before examination with a Siemens 101 electron microscope (Siemens Corp., Iselin, N. J.).

Tissues were examined grossly for metastasis, embedded in paraffin by the usual procedure, and stained with hematoxylin and eosin. All data were examined by Student's t test, and a p value less than or equal to 0.05 was considered significant. Data were expressed as mean ± S.E.

RESULTS

The effect of the MtT-F4 tumor on organ growth has been well characterized in the literature (3, 10), but characteristics of our tumors will be described briefly. The size of the changed tumor was significantly larger than that of the unaltered one (Table 1). Occasional ulcerations of the skin surrounding the tumor were observed, although both tumors appeared to be well encapsulated. The tumor caused compression of muscle fibers because of its large size, although the tumor did not infiltrate among the muscle fibers.

The adrenal glands from animals bearing the unaltered tumor in Group 2 were significantly larger than those from...
Table 1
Effect of 2 MtT-F4 tumors on organ weights in Fischer F344 rats

Two strains of a mammotrophic pituitary tumor were studied, one producing considerable ACTH (Group 2) and the other (Group 1) producing a smaller quantity of hormone. Control non-tumor-bearing animals were in Group 3. Animals were sacrificed at 6 weeks after implantation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>Tumor wt (g)</th>
<th>Adrenal (mg)</th>
<th>Liver (g)</th>
<th>Spleen (mg)</th>
<th>Heart (mg)</th>
<th>Kidney (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>380 ± 10*</td>
<td>133 ± 5</td>
<td>337 ± 18</td>
<td>38.5 ± 2.3</td>
<td>1713 ± 242</td>
<td>1327 ± 33</td>
<td>1834 ± 71</td>
</tr>
<tr>
<td>2</td>
<td>315 ± 5</td>
<td>67 ± 6*</td>
<td>813 ± 58*</td>
<td>36.2 ± 1.4</td>
<td>638 ± 95*</td>
<td>1406 ± 70</td>
<td>4072 ± 784*</td>
</tr>
<tr>
<td>3</td>
<td>168 ± 3</td>
<td>53 ± 2</td>
<td>53 ± 2</td>
<td>6.2 ± 1.5</td>
<td>371 ± 11</td>
<td>634 ± 85</td>
<td>1261 ± 61</td>
</tr>
</tbody>
</table>

* Mean ± S.E.
*p < 0.001 (Group 1 versus Group 2).

DISCUSSION

A variant of the MtT-F4 tumor was obtained after 10 passages of the tumor in Fischer F344 rats. Metastasis arising from the altered tumor was observed in retroperitoneal lymph nodes in tumor secreting ACTH or reduced ACTH. This is the first report of metastasis in mammothropic pituitary tumor-bearing animals insofar as we can determine.

We suggest that secretion of ACTH became reduced because adrenal weight was significantly smaller than that in rats bearing the unaltered tumor. The increased size of the tumor and apparent reduction in ACTH secretion suggest that the tumor parenchymal cells became less differentiated. A similar loss of differentiation and ability to secrete ACTH was observed with ACTH-producing tumor cells by Sato and Buonassissi (15) in cells maintained in tissue culture. Previous investigators have pointed out that transplanted tumors may undergo modification in the hormones secreted by the cells during passages (8). Our results do not permit us to explain the mechanism of metastasis in the MtT-F4 tumor. The tumor also produces growth hormone and prolactin (2), although we do not know from our studies whether or not the secretion of these hormones is reduced.

It is interesting that the metastases were confined to lymph nodes. It is possible that the tumor produced metastasis to other organs and that these implants could not be detected microscopically because there was not sufficient time for tumor growth to occur. Growth of the tumor for a longer period is not possible because of severe wasting of the animals after 6 weeks of tumor growth.

Alteration in tumor did not produce a detectable change in the ultrastructure of the tumor. Several investigators (12, 13, 16) have described the ultrastructure of the MtT-F4 tumor. The tumor is chromophobic, having an adenomatous pattern. It is not surprising that we could not detect changes in tumor by morphology alone. Although it is assumed that different cell types produce growth hormone and prolactin in the tumor (4, 6, 18), the absence of distinct secretory granules is a disadvantage, inasmuch as granules are particularly useful for identification of cell types in the anterior pituitary gland (1, 7).

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Fig. 1. Metastatic tumor parenchymal cells in a lymph node. The cells contain no secretory granules. Numerous elongated mitochondria (M) occupy a large portion of the cytoplasm. Cells border a lumen (L). The cytoplasm contains numerous polysomes (arrow) but contains only a few rough cisternae of endoplasmic reticulum (double arrow). One cell is in mitosis; LY, lysosome. In the inset, a 1-μm section is stained with toluidine blue and shows a portion of the lymph node with lymphocytes (LM) and adjacent tumor cells (T) forming a lumen. × 11,600; inset, × 250.
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