THE THYROXIN PRODUCTION IN METASTASES FROM CARCINOMA OF THE THYROID

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It seems unquestionable that a production of active thyroid colloid may take place in tumors arising from the epithelium of the thyroid gland. This has been proved experimentally for adenomata by Johan Holst, and would appear to be true also of carcinomata. Thus myxoedema is not found in association with carcinoma of the thyroid, at least in any except atypical forms (Bérard and Dunet, 1). Even in cases in which the thyroid is found at autopsy to be entirely replaced by tumor tissue, no history of myxoedema is obtained (Borst, 2; Johan Holst, 3). Occasionally symptoms of hyperthyroidism or dysthyroidism occur.

These observations, however, are not entirely convincing inasmuch as there cannot be excluded with certainty the occurrence of islands of normal cells or of aberrant glands with a normal or increased colloid production. For this reason, a study of the biological qualities of the metastases from tumors primary in the thyroid offers valuable information. Such a case was reported by v. Eiselsberg (3) in 1894. In a thyroidectomized patient myxoedema developed. Two years later a tumor appeared in the manubrium sterni, whereupon the symptoms disappeared. The tumor was removed and on histologic examination proved to be a carcinoma of the thyroid with cylindrical cells and a colloid content. After operation the myxoedema reappeared. Similar observations have been reported by other writers.

At the Norwegian Radium Hospital we have, in two cases, undertaken a biological demonstration of thyroxin in metastases from carcinoma of the thyroid, and as such an investigation may in some cases be of diagnostic value, the cases are presented here.

CASE I: An eighty-two-year-old woman had for twenty years a goiter which had remained stationary. A year prior to entering the hospital she had noticed a swelling at the back of the head, which subsequently increased in size. She was operated upon Oct. 7, 1932, and was informed that a tumor was found arising "from the brain." It was not possible to remove all the tumor tissue.

On Dec. 2, 1932, the patient entered the Norwegian Radium Hospital. Examination revealed a well defined tumor, 5 × 8 cm., corresponding to the thyroid gland, somewhat movable in relation to the underlying tissue and with freely movable skin above. At the back of the head, approximately in the middle line, was a firm swelling, not sharply defined, about 6 cm. in diameter. A defect in the cranium could be palpated at this site. The pulse was 72. There was no tremor or exophthalmos. Graefe's and Moebius' signs were positive. There was neither paralysis nor disturbance of sensibility. Reflexes were normal.

On x-ray examination of the cranium there was found near the middle of the lambdoid suture a circular defect 5 to 6 cm. in diameter with a somewhat jagged outline. No periosteal reaction was observed, and there was no sign in the roentgenogram of increased intracranial pressure. X-ray diagnosis: Tumor destruction in the cranium, probably a metastasis.

The microscopic report on the specimen from the operation of Oct. 7 was as follows
(Dr. Kreyberg): Between fibrous bundles and small areas of bone tissue, there is tumor tissue distinguished by cells some of which are without sharp boundaries, with round-oval nuclei containing finely distributed chromatin substance and no distinct nucleoli. In some areas the cells occur in more compact clumps and bands and in some they form distinct alveoli and assume a cuboidal appearance. In many places the alveoli contain colloid substance which stains with eosin and hematoxylin. Histologic diagnosis: Metastasis from adenocarcinoma of the thyroid (Fig. 1).

Pieces of the cranial metastasis were then examined for thyroxin, by Mr. G. Bøe, M.Sc. The method used was based on the observation that thyroxin in white mice increases the resistance to acetonitril (Hunt, 6). The test animals used had been for three weeks on a diet of oats and had a resistance to acetonitril of 0.35 mg. If the animals received 0.01 mg. of sodium thyroxin by mouth, the resistance was increased by about 400 per cent. It was found that 0.2 c.c. of a 4 per cent suspension of the dried tumor tissue dry material) raised the resistance from 0.35 to more than 2 mg. acetonitril per gm. of body weight, in other words, by more than 400 per cent.

This patient was treated with x-rays, some 3450 r being given to the thyroid gland through two fields and 1350 r to the metastasis. Some improvement took place, but the cranial tumor increased in size and new metastases appeared. The patient is still alive, three years after treatment, and the malignant goitre still remains stationary.

Case II: A sixty-four-year-old woman had a goitre present from youth. It had remained unchanged or, in the patient’s opinion, had even diminished somewhat in size. A year previously a tumor was discovered on the back of the right thigh, and this had grown steadily.

The patient entered the Radium Hospital on July 9, 1935. A small goitre was found, localised chiefly in the left lobe and isthmus. It was easily movable, the surface was smooth, there was no infiltration of the surrounding parts, and no hard areas were present.

On the right thigh was a tumor the size of a baby’s head. It was very prominent and the overlying skin was bluish-red, easily movable, with distinct venation. The tumor was of the consistence of india rubber, and for the most part sharply outlined. It was movable with the soft parts of the thigh, to which it seemed to be adherent. No bone lesion could be demonstrated by x-rays, apart from a slight periostitis.

A piece of the tumor was excised for microscopic examination, and the report was as follows (Kreyberg): A polymorphous tumor tissue with an abundance of cells and blood-
vessels. The cells are of varying sizes, mostly irregular and polygonal. Multinuclear cells and occasional cells with large, irregular, and hyperchromatic nuclei are present. The tumor cells show phagocytic properties. Not a few have a finely vacuolised cytoplasm resembling lipid macrophages. Histological diagnosis: Very atypical malignant tumor. Sarcoma? Metastasis from an endocrine gland? (Fig. 2.)

The patient was treated with x-rays, 4,000 r distributed over two fields being given to the thigh tumor. As this treatment had no demonstrable effect, and as it had not been possible to establish the existence of other metastases, disarticulation at the hip joint was performed, and the tumor was again examined microscopically (Kreyberg).

In view of the histologic findings, it was still thought that the tumor might be a metastasis from a malignant tumor in an endocrine gland, possibly a carcinoma of the thyroid. Pieces of the tumor were therefore removed for biological examination for thyroxin (Mr. F. Bøe, M.Sc.). The strain of test animals used had been on a diet of oats for three weeks and had a resistance to acetonitril of 0.4 mg. per gm. body weight; administration by mouth of 0.01 mg. thyroxin increased the resistance by 200 per cent, from 0.4 to 1.2 mg. per gm. body weight.

By administration of 0.2 c.c. of a 4 per cent suspension of the dry tumor tissue, corresponding to 0.008 gm. of dry substance, the resistance was raised from 0.4 to 1.2 mg. acetonitril per gm. body weight, in other words 200 per cent. The biological effect of 0.008 gm. dry substance thus corresponds to 0.01 mg. thyroxin and consequently 1 gm. of dry substance to 1.65 mg. thyroxin.

On account of this finding, teleradium treatment was administered to the thyroid, through three fields, 41.6 + 37.7 + 17.4 Dominici units being given. At the end of the treatment the thyroid was somewhat decreased in size and softer. The neck circumference was reduced by 2 cm.

**Discussion**

In both of these cases the diagnosis presented considerable difficulty. In the first case, to which reference has been made in a previous paper (4), we were compelled by the clinical and roentgen findings to assume the existence of a metastatic tumor, but no definite conclusions could be drawn as to its origin. It is true that there was a goitre, but this had remained stationary for twenty years and on examination it showed no signs of malignancy. On the basis of the histologic appearance of the metastasis, the conclusion could be drawn, however, that the primary tumor must be a carcinoma of the thyroid, and this was confirmed by the biological demonstration of thyroxin in the metastasis.

In the other case the diagnostic difficulties were even greater. From the clinical and x-ray findings it could not be determined whether the tumor in the thigh was primary or metastatic. Here also a goitre was present, but this had remained stationary for thirty to forty years and showed no sure signs of malignancy. We were, therefore, inclined to regard the tumor in the thigh as primary, probably a sarcoma originating from the soft parts.

The histologic findings indicated only that we were dealing with a very atypical malignant tumor, but whether it was a sarcoma or a metastasis from an endocrine gland could not be decided. As the tumor proved to be radio-resistant, it was taken for granted that it was probably a fibrosarcoma arising from the fascia. Since, however, the pathologist had pointed to the possibility of a metastasis from an endocrine gland, possibly the thyroid, a biological investigation for thyroxin was undertaken. All things considered, however, the positive result of this examination was rather surprising. In this case it would have been quite impossible, on the basis of the clinical and histologic
findings, to make a correct diagnosis. This was possible only by demonstration of thyroxin in the tumor in the thigh.

The determination of thyroxin in carcinoma metastatic from the thyroid is of both theoretical and practical importance. Its theoretical importance lies in the fact that it shows that tumor cells emanating from the thyroid epithelium really produce thyroxin. An examination of the primary thyroid tumor itself will always leave one in doubt, since, as previously stated, it is not possible to exclude the presence of islands with a normal gland epithelium. In a metastasis this possibility of error does not exist. The practical importance of the test lies in the fact that it offers a possibility of proving a tumor to be a metastasis from a carcinoma of the thyroid in cases in which other convincing evidence is lacking, even where the histological findings are decidedly atypical.

In our second case, apart from the diagnostic problem there is another point which should be emphasized, that is, that the tumor was radioresistant. We are accustomed to consider a strongly atypical and undifferentiated tumor, such as the one under discussion, as radiosensitive. But in carcinoma of the thyroid it appears, as others have reported, that a very slightly differentiated tumor may be less radiosensitive than the more differentiated growths.

The biological demonstration of thyroxin is based on the fact that this substance induces in mice a considerably increased resistance to acetonitril, a circumstance which is proved in a number of papers by Hunt. It is not necessary to deal at length with these investigations, but I will mention briefly the method of procedure which was followed in the two cases reported.

The pieces of tissue are cut into small fragments and allowed to stand
overnight in acetone. The following day they are transferred to a Soxhlet apparatus and extracted for twenty-four hours in acetone, and if necessary a further twelve hours in petrol ether (boiling point 30°–50° C.). After drying in a vacuum exsiccator, the tissue is pulverised sufficiently fine for making a 4 per cent suspension, which is used for the further biological investigation.

White male mice are used, which have been limited to an oat diet for three weeks. To determine the toxic dose of acetonitril an intravenous injection of 10 per cent acetonitril in a physiological saline solution is given after the animals have fasted for two hours. The animals are examined twenty-four hours after the injection. In our case No. 2, 20 mice were used for this test and the toxic dose was fixed at 0.4 mg. per gm. body weight.

A second series of animals is tested to determine how much the toxic dose is raised by the oral administration of 0.01 mg. thyroxin. On the first day, after the animals have fasted two hours, an injection is given of 0.2 c.c. of a solution containing 0.01 mg. thyroxin through a tube, by mouth. On the following day, also after a fast of two hours, an intravenous injection of acetonitril is given, as in the first series, and the animals are then examined after the lapse of twenty-four hours. In our case No. 2, 14 animals were used for this test and the resistance was found to be increased by 200 per cent.

The third series of experiments is carried out in the same manner except that, instead of a solution of sodium thyroxin, a 4 per cent suspension of the dry tumor tissue is used, 0.2 c.c. being administered by mouth. In case No. 2, for which 20 animals were used, the resistance was raised by 200 per cent, which corresponds to 0.01 mg. thyroxin. As 0.2 c.c. of the 4 per cent suspension is equivalent to 0.008 mg. dry substance, this means that 1 gm. of the tumor tissue biologically corresponds to 0.33 mg. thyroxin.

It is clear from this description that the investigation requires considerable work and a fairly large number of test animals if reliable results are to be obtained. On the other hand, the result is of great importance, since a metastasis from thyroid carcinoma is often solitary. By energetic radiological treatment of the primary tumor and the metastasis, or by combined radiological and surgical treatment, there will often be a chance of essentially lengthening the life of the patient.

References