STUDY OF THE CONCENTRATION OF ORGAN-SPECIFIC ANTIGEN (THYROGLOBULIN) IN THE HUMAN THYROID AND ITS TUMORS

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G. I. Avdeev and M. I. Gel'bshtein

Virological Laboratory (Head, Professor V. V. Gorodilova) and Pathologo-Anatomical Division (Head, Cand. Med. Sci. Z. V. Gol'bert), P. A. Gertsen Oncological Research Institute (Director, Professor A. N. Novikov), Moscow
(Presented by Active Member AMN SSSR L. A. Zil'ber)
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During the study of the antigenic simplification of human tumors we found that this phenomenon is exhibited differently in different tumors: whereas it is usually impossible to find organ-specific stomach antigens in the tissues of malignant growths of the human stomach [1], the organ-specific antigen of the thyroid gland is clearly demonstrable in almost all tumors of this organ. An investigation of certain properties of this antigen led us to the conclusion that it is thyroglobulin, the immunological behavior of which has been studied in detail by other investigators [5].

It is known that a considerable proportion of thyroid tumors are much less able to accumulate iodine than normal thyroid tissue. Thyroglobulin is the chief iodine-containing protein of the gland. Accordingly, we were not content merely to demonstrate the presence of thyroglobulin in most thyroid tumors, but we also compared the concentration of thyroglobulin (in other words, of organ-specific antigen) in normal thyroids and in thyroid tumors, including varieties absorbing iodine readily and others absorbing little or no iodine.

METHOD

Antithyroid serum, obtained by immunization of a rabbit with a saline extract of human thyroid gland, was exhausted by addition of a mixture of human sera, and also of extracts of liver and spleen. This serum gave an organ-specific reaction in Ouchterlony's test only with thyroid extract, and did not react with antigens from the spleen, kidney, liver, lung, and gastric mucosa.

By means of the precipitation reaction in agar, this serum was used to titrate saline extracts (1 part tissue and 4 parts physiological saline) of normal thyroid glands and of tumors of the thyroid. Serial two-fold dilutions were used for the titrations, and the maximal dilution of antigen still giving a precipitation line with the particular serum was noted. Since the protein concentration in the extracts varied slightly, the protein concentrations (number of micrograms of protein in 1 ml) and not the titers were determined in the maximal dilution of antigen giving a reaction.

Data concerning the accumulation of radioactive iodine by tumors were kindly made available for use by N. V. Obukhov, on the staff of the radiological division of this institute. The results of scintillography were recorded as follows: − no accumulation of iodine observed, + slight accumulation, +++ near normal accumulation of iodine, X scintillography not carried out.

Besides these indices, data were also obtained in respect of the presumed accumulation of iodine based on the study of the morphology of the tumors. In a recently published autoradiohistographic study of a large number of thyroid tumors removed from patients receiving radioactive iodine before operation, M. I. Gel'bshtein showed that tumors consisting of follicular and folliculo-alveolar structures possess the ability to accumulate iodine. The degree of accumulation of iodine depends on the functional state of the follicles and their degree of differentiation [2]. As a result of experience gained during this investigation the histological study of a tumor could now be used to evaluate the ability of this tumor to accumulate iodine, with a high degree of reliability. This suggested scale of evaluation was as follows: − tumor unable to accumulate iodine, ± accumulation of iodine absent or very slight, + slight

Results of Titration of Antigens from Thyroid Tumors with Organ-Specific Antithyroid Serum

Histological type of tumor	Minimal concentration of antigen giving reaction (in μg protein)	Presumed accumulation of iodine	Results of scintillography
1. Metastasis of tumor No. 6 . . .	<5000	–	–
2. Anaplastic carcinoma	<1600	–	×
3. Keratinizing squamous-cell carcinoma	<1800	–	–
4. Embryonic adenoma.	1125	+	+
5. Malignant papillary adenoma.	778	–	×
6. Undifferentiated small-cell carcinoma	687	–	–
7. Malignant papillary adenoma, small number of follicles . .	550	±	–
8. Undifferentiated small-cell carcinoma	362	–	×
9. Carcinosarcoma	288	–	+
10. Langhans' goiter with marked anaplasia of cells and small follicles	206	+	×
11. Malignant adenoma, mainly papillary.	187	±	+
12. Malignant adenoma, mainly papillary, with single follicles	88	±	–
13. Metastasis of tumor No. 14 . .	56	+++	+
14. Folliculo-alveolar adenocarcinoma, partly papillary.	28	++	–
15. Adenoma, part fetal, part embryonic.	22	++	+++
16. Metastasis of folliculo-alveolar adenocarcinoma . .	21	++	–
17. Malignant adenoma, mainly papillary.	20	±	–
18. Metastasis of tumor No. 7 . . .	9	±	–
19. Malignant papillary adenoma (mixed type)	8	++	×
20. Colloidal microfollicular adenoma.	4.8	++++	×

accumulation, ++ considerable accumulation, +++ intensive accumulation corresponding to the accumulation of iodine by the normal thyroid, ++++ very intensive accumulation of iodine.

RESULTS

Titration of extracts of normal thyroids gave the following results. These antigens reacted with antithyroid sera in dilutions of between 6.6 and 62 μg/ml (62, 54, 54, 34, 33, 24, 21, 14, 14, 12, 8, and 6.6 μg/ml). Hence, the thyroglobulin concentration in normal thyroids varies considerably. However, as the table giving the results of titration of the tumor extracts shows, their concentration of thyroglobulin varies still more. Besides the tumors whose extracts, like the extracts of the normal thyroid glands richest in thyroglobulin, reacted in dilutions of up to 5-8 μg/ml, the extracts of three tumors (Nos. 1, 2, and 3) did not react with the antithyroid serum even in the undiluted form. Of the 20 tumors tested, in 12 the thyroglobulin concentration was lower than in the normal thyroid

gland with the least thyroglobulin. Hence, total loss of organ-specificity by thyroid tumors was rare. A far more frequent finding was some degree of lowering of the concentration of organ-specific antigen, similar to that found during the study of hepatomas of mice [3].

The results of scintillography demonstrated that the ability to accumulate iodine was depressed in almost all the tumors studied. No difference was found between the groups with normal or a diminished thyroglobulin concentration. Whereas in the first group accumulation of iodine was observed in 2 of the 6 tumors studied, in the second group it was found in 3 of the 8 tumors studied.

A definite relationship was discovered between the concentration of organ-specific antigen and the histological structure of the tumor. The results given in the table show that, morphologically speaking, the tumors with a low thyroglobulin concentration belonged to the group exhibiting little or no accumulation of iodine, i.e., not forming follicular or folliculo-alveolar structures, characterizing ability to synthesize colloid. Tumors accumulating iodine intensively belonged mainly to the group with a relatively high thyroglobulin concentration.

The results of scintillography seem to conflict with the estimates of iodine accumulation made on the basis of the study of the tumor morphology. The most likely explanation is that the indices of scintillography are fairly rough: they simply show that the accumulation of iodine is lower than normal. The estimates based on the morphology, on the other hand, can indicate the finer gradations of diminishing ability of the tumor tissues to accumulate iodine.

The comparative study of the ability of the tumors to accumulate iodine and of their thyroglobulin concentration disclosed a certain parallel between the values of these factors. A low thyroglobulin concentration in a tumor was usually associated with low powers of iodine accumulation, while tumors with a normal thyroglobulin concentration absorbed iodine comparatively readily. This parallel is understandable because thyroglobulin is the chief iodine-containing protein of the thyroid. However, only a certain parallel was observed between these indices, and not a strict correlation. Ability to absorb iodine was found to be sharply reduced, not only in tumors poor in thyroglobulin, but also in most of the tumors with a normal concentration of this protein. The most likely explanation of this fact is that the iodine absorbed by the thyroid is initially taken up, not by thyroglobulin, but by other proteins bound with the granules in the cytoplasm of the thyroid cells [4].

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