ANTIGENIC SIMPLIFICATION OF THYROID TUMORS

B. S. Sinyakov, G. I. Avdeev, M. I. Gel'bshtein, and N. V. Obukhov

UDC 616.441-006.-07:616.441-008.9-097.2-078.73

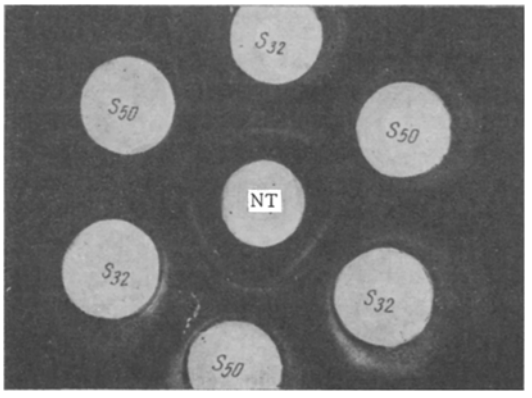
Some tumors lose their organ-specific antigens characteristic of the normal tissue from which they were derived. It has been shown by the use of labeled antibodies that thyroid tumors lose their organ specificity, and in fact, that they lose their microsomal antigen [10]. This result confirms earlier observations [15].

In the present investigation the content of organ-specific thyroid antigen—thyroglobulin—was studied in the normal thyroid and in the thyroid affected by a malignant tumor. The intensity of accumulation of iodine by malignant thyroid tissue was also studied.

EXPERIMENTAL METHOD

Thyroid glands affected by tumors and pathological changes were obtained from the operating theater, and normal tissues from cadavers of persons dying from injury. The material was kept at −15°. Saline extracts of the normal and pathological thyroids were prepared in proportions of 1 part of tissue to 3 parts physiological saline. The protein concentration (in μg/ml) in the maximal dilution of antigen still giving a reaction was determined. The micromodification of Ouchterlony's precipitation reaction was used [4].

On the basis of results showing that antibodies are present in the sera of persons with certain thyroid diseases [11-13, 16], human autoimmune organ-specific thyroid antisera were used in the investigation. Two sera used were obtained from women with Hashimoto's disease treated by hormones. Both sera reacted organ-specifically, but their reactions were not completely identical. It is clear from the figure, showing the spurs which were formed, that the sera were not completely identical but were found to contain different components of thyroglobulin. This reaction demonstrates the complex structure of thyroglobulin [2].



Comparison of two autologous thyroid antisera. The central well contains an extract of normal thyroid gland; the pheripheral wells contained the sera of two patients with Hashimoto's disease (S_{32} and S_{50}).

On the basis of the morphological structure of the tumors, the intensity of iodine accumulation by the tumor tissue can be foretold with reasonable probability. It has been shown that more iodine is accumulated by tumors consisting of follicular and a combination of follicular and alveolar structures, and that the degree of accumulation in turn depends on the functional state of the follicles and on their differentiation [3]. The supposed accumulation of iodine (I^{131}) in thyroid tumors was assessed, radioisotope scanning, as widely used in clinical practice [6, 9] was carried out, and the relative accumulation of radioactive phosphorus (P^{32}) in the tumors was determined.

EXPERIMENTAL RESULTS

Altogether 66 thyroids were investigated, of which 12 were normal, 23 contained tumors, 20 were nodular (cystic and colloid goiters), and 11 were thyrotoxic.

Laboratory of Immunology, Departments of Pathological Anatomy and Radiology, P. A. Gertsen Moscow Oncologic Institute (Presented by Active Member of the Academy of Medical Sciences of the USSR, L. A. Zil'ber). Translated from Byulleten' Éksperimental' noi Biologii i Meditsiny, Vol. 63, No. 5, pp. 80-84, May, 1967. Original article submitted April 19, 1966.

Results of Investigation of Human Thyroid Tumors

Historical form of tumor	Minimal concentration of antigen giving reaction (in μg protein/ml)	Supposed accumulation of iodine	Results of scanning	
			accumulation of radioactive iodine	accumulation of radioactive phosphorous
	1	2	3	4
Papillary cystadenocarcinoma	> 8 800	±	−	+
Microfollicular malignant adenoma with emptying of follicles	> 6 900	+ + +	+	+
Metastasis of a solid alveolar carcinoma in a lymph gland	> 5 800	±	−	+
Metastasis of a sclerosing solid carcinoma in a lymph gland	> 5 500	±	×	×
Microfollicular adenoma with metaplasia	> 4 200	+	−	+
Solid alveolar carcinoma	4 200	−	−	+
Solid follicular carcinoma	> 3 200	+	×	×
Papillary adenocarcinoma	2 900	−	×	×
Solid alveolar carcinoma	2 775	+	+	+
Metastasis of a sclerosing, predominantly papillary carcinoma in a lymph carcinoma in a lymph gland	> 2 700	+	+	+
Follicular adenocarcinoma	2 600	+ +	×	×
Glandular carcinoma with individual follicles	> 2 300	+	−	−
Papillary follicular carcinoma	2 150	+	−	+
Solid carcinoma	> 2 100	−	−	+
Anaplastic carcinoma	2 000	−	×	×
Struma of Langhans	1 950	±	+	−
Papillary carcinoma with follicles	1 700	+	−	+
Follicular solid carcinoma with many follicles	1 375	+ + +	×	×
Malignant adenoma	1 125	+ + +	×	×
Solid carcinoma with areas of struma of Langhans	675	±	×	×
Malignant follicular parenchymatous adenoma	362	+ + +	−	+
Follicular solid carcinoma	300	+ + +	×	×
Metastasis of malignant papillary adenoma in a lymph gland	218	+ +	−	+

Legend: in column 2: −tumor does not accumulate iodine, ± very slight accumulation, + slight accumulation, + + considerable accumulation, + + + normal accumulation; in columns 3 and 4: - no accumulation, + accumulation found; × scanning not performed.

By titrating the antigens from the normal and pathological thyroids with two organ-specific sera from patients with thyroiditis, results were obtained reflecting the content of thyroglobulin in these tissues.

The extracts of the normal glands reacted with serum No. 32 in protein concentrations from 1112 to 169 μg/ml. Of the 23 extracts of thyroid tumors, 9 did not react at all 9 reacted in protein concentrations from 4200 to 1375 μg/ml, i.e., the thyroglobulin concentration was lower than in the normal gland with the lowest content of thyroglobulin, and 5 reacted in the same protein concentrations as normal thyroid glands (1125-218 μg/ml).

Statistical analysis of these results showed that the content of thyroglobulin in the thyroid tumors differed from that in the normal thyroid glands by a statistically significant degree ($P < 0.01$ from Student's table [5]).

The differences between the thyroglobulin content in normal tissues, and in the nodular and thyrotoxic thyroid glands were not statistically significant.

Similar results were obtained with serum No. 50.

Complete loss of the organ-specific antigen—thyroglobulin—by the thyroid tumors was therefore rarely seen, and even the phenomenon of antigenic simplification was quantitative in character. A definite relationship was found between the content of thyroglobulin in the tumor and its histological structure (see table).

The table shows that most tumors with a low thyroglobulin content were morphologically undifferentiated forms, without follicular or alveolar structures, and incapable of forming colloid. They accumulated little or no iodine. The group with the higher content of thyroglobulin consisted of tumors whose morphology demonstrated their ability to accumulate iodine well. The results of scanning showed that the ability to accumulate radioactive iodine was depressed in nearly all the malignant thyroid tumors. This discrepancy between the results for the accumulation of iodine by thyroid tumors obtained on the basis of the morphological characteristics and by the method of scanning may evidently be attributed to the comparatively low sensitivity of the scanning technique.

The incomplete agreement between the results for the thyroglobulin content and the ability of the tumors to absorb iodine may be attributable to the fact that in some cases different parts of the tumors, both morphologically and functionally, were subjected to histological and immunological investigation. The iodine absorbed by the thyroid is known to be bound initially, not with thyroglobulin, but with the cytoplasmic microsomal antigen [8]. It is interesting that malignant change in the thyroid was accompanied not only by a decrease in the ability to accumulate iodine, but also by an increase in the accumulation of phosphorus. The increased accumulation of radioactive phosphorus by thyroid tumor tissues reflects the increased metabolism and the increased mitotic activity of their cells [7]. This in turn shows that the decrease in the absorption of iodine by thyroid tumors is specific in character and cannot be explained by the development of necrosis or by other similar causes.

The results obtained by the use of autologous sera of patients with Hashimoto's disease thus confirmed earlier results obtained by the authors using thyroid antisera from rabbits [1]. These results show that in most thyroid tumors the thyroglobulin content is below normal and that this decrease to a certain extent runs parallel to the decrease in the ability to accumulate radioactive iodine. No decrease in the content of this organ-specific antigen is observed in several other thyroid diseases.

LITERATURE CITED

1. G. I. Avdeev and M. I. Gel'bshtein, Byull. Éksp. Biol., No. 11, 99 (1964).
2. G. I. Avdeev, Byull. Éksp. Biol., No. 6, 77 (1965).
3. M. I. Gel'bshtein and N. V. Obukhov, Med. Radiol., No. 9, 32 (1963).
4. A. I. Gusev and V. S. Tsevtkov, Lab. Delo, No. 2, 43 (1961).
5. L. S. Kaminskii, Analysis of Clinical and Laboratory Data [in Russian], Leningrad (1959), p. 123.
6. N. V. Obukhov, Med. Radiol., No. 6, 3 (1965).
7. Yu. A. Umanskii, The Accumulation of Artificial Radioactive Phosphorus in Tumors, Candidate Dissertation, Kiev (1951).
8. L. J. DeGroot and E. Carvalho, J. biol. Chem., 235, p. 1390 (1960).
9. A. Gandy and H. Jammet, Proceedings of the Second International Conference on the Peaceful Use of Atomic Energy, 9, Selected Papers by Foreign Scientists, Radiobiology and Radiation Medicine [in Russian], Moscow (1959), p. 394.
10. R. B. Goudie and H. M. McCallum, Lancet, 2, 1035 (1963).
11. I. M. Roitt, D. Doniach, P. N. Campbell, et al., Lancet, 2, 820 (1956).
12. I. M. Roitt, P. N. Campbell, and D. Doniach, Biochem. J., 69, 248 (1958).
13. I. M. Roitt, D. Doniach, in the book: Mechanisms of Antibody Formation, Prague (1960) p. 70.

14. E. Witebsky, N. R. Rose, and S. Shulman, J. Immunol., 75, 269 (1955).
15. Idem , Cancer Res., 16, 831 (1956).
16. E. Witebsky, N. Rose, K. Terplan, et al., J. A. M. A., 164, 1439 (1957).