Evidence of autoimmune pathogenesis in autonomous thyroid adenoma

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Abstract. Using an immunohistochemical attempt to immunostain thyroid related autoantibodies, 30 specimens of autonomous adenomas of the thyroid were investigated. Twelve out of 23 inflammatory infiltrates surrounding the 'hot' nodules contained plasma cells, which gave a positive staining reaction for thyroid related autoantibodies. Seven adenomas showed no significant lymphoplasmacellular infiltration. It is concluded that this phenomenon might be due to an autoimmune pathogenesis in a part of patients with autonomous adenomas, indicating that there is no sharp line between autoimmune and non autoimmune thyroid disorder.

It is generally accepted that hyperthyroidism in Graves' disease is caused by autoantibodies directed against determinants on thyroid epithelium, which are synthesized within the lymphoplasmacellular infiltrates of the thyroid gland itself (Mclachlan 1983). Nevertheless, inflammatory infiltrates of similar quality and quantity occur on euthyroid hyperthyroid nodular goitres too. Are these infiltrates a sign of autoimmunity? As the serum activity of thyrotropin displacing autoantibodies is considered to be due to an 'overflow' from the affected thyroid gland it is conceivable that in a number of cases only the direct proof of autoantibodies on hyperfunctioning tissue itself will make it possible to distinguish between and autoimmune and non-autoimmune thyroid disorder.

Material and Methods
Formalin-fixed and paraffin-embedded tissue sections of 30 autonomous thyroid adenomas were prepared conventionally for immunohistochemistry. Then slices were incubated with a porcine thyrotropin receptor containing membrane preparation (pTSH-R). In a second step slices were incubated with an antibody to pTSH-R obtained from immunized rabbits. Finally the tissue sections were processed with the customary peroxidase antiperoxidase technique according to Sternberger (1979), using goat anti-rabbit IgG as bridge antibody. End product of the staining procedure is a brown agent. The method is described in detail elsewhere (Sellschopp et al. 1986).

The specificity of the staining reaction for thyroid related autoantibodies was confirmed by

1) Omitting the incubation with rabbit anti-pTSH-R.
2) Omitting the incubation with pTSH-R itself.
3) Absorption of pTSH-R to serum with high TSH displacing activity prior to its application on staining procedure.
4) Incubation of pTSH-R with serum of a patient with high titres of microsomal antibodies (Hashimoto's disease) prior to the staining procedure.

For negative controls, the immunostaining procedure was extended to thyroid lobes centralateral to a differentiated thyroid carcinoma, to Hashimoto's thyroids and to normal tonsils of patients without any thyroid disorder.

Results
Immunohistochemical tests using pTSH-R revealed an intensive brown staining of the cytoplasm of a considerable portion of plasma cells within the inflammatory infiltrates in 12 out of 23 autonomous thyroid adenomas. (Figs. 1 and 2). Seven adenomas were not surrounded by infiltrates. In negative controls the omission of pTSH-R led to negative results.
**Fig. 1.**
Infiltrate within an autonomous thyroid adenoma: positive staining reaction of plasma cells (arrows), PAP-immunostaining using pTSH-R, nuclear counterstaining with haematoxylin, × 400.

**Fig. 2.**
Detail of Fig. 1 at higher magnification PAP-immunostaining using pTSH-R, nuclear counterstaining with haematoxylin, × 1000.
R or anti-pTSH-R led to a significant reduction of staining intensity up to only a slight background being visible.

Absorption of pTSH-R to serum containing TSH displacing activity reduced the staining intensity of plasma cells significantly. Pre-incubation of pTSH-R with Hashimoto's serum did not influence the staining reaction. Lymphatic cells of thyroid lobes contralateral to carcinoma, of Hashimoto's thyroid and of normal tonsils were not stained.

**Discussion**

Lymphoplasmacellular infiltrates of the thyroid may occur in patients with euthyroid and hyperthyroid nodular goitres as well as in patients with Graves' disease (Mortensen et al. 1955; Williams & Doniach 1962; Hofstätter et al. 1978; Yoshida et al. 1978). Activated T-lymphocytes with a local relationship to HLA-DR positive thyroid epithelia and macrophages in the periphery of autonomous functioning adenomas could be demonstrated by Grubeck-Loebenstein et al. (1985). Considerable disagreement exists, whether such findings should be regarded as a correlate of an autoimmune thyroid disorder. The distribution pattern of IgG producing plasma cells within Graves' thyroid and within eu- and hyperthyroid goitres is quite similar (Lawerenz et al. 1984). Using our method it could be demonstrated that these IgG bind pTSH-R, not only in Graves' disease as shown previously (Sellschopp et al. 1986), but on more than half of the investigated autonomous adenomas too. We conclude that the pTSH-R mediated staining of the intrathyroidal plasma cells is due to their synthesis of autoantibodies directed against TSH receptor related structures of thyroid epithelia. Although the stimulating capacity of the stained Ig cannot be proven by pure morphological techniques, it is probably pertinent to consider that these autoantibodies found in hyperfunctioning thyroid tissue represent TSI. Our findings on specimens of autonomous adenomas may indicate that there is no sharp line between autoimmune and non-autoimmune thyroid disease.

Based on our results we prefer to recommend the subtotal resection of the affected thyroid lobe.

In case of single enucleation there is a probability of leaving infiltrates, which could lead to a recurrence of the autonomous thyroid adenoma.

**References**


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