Cushing's syndrome
and autonomous thyroid nodules, a variant
of multiple endocrine neoplasia?

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Abstract. Over a 20 year period 4 of 40 (10%) female patients with Cushing's syndrome also had a solitary thyroid nodule. In 3 cases this was an autonomous 'hot' nodule. In the same population only one case of presumed Graves' disease was seen. It is postulated that the association of autonomous thyroid nodule and Cushing's syndrome may represent a variant of multiple endocrine neoplasia.

Because of the clinical suspicion that solitary thyroid nodules occurred relatively commonly in patients with Cushing's syndrome, we reviewed the case sheets of 50 consecutive patients with this condition who had attended the Endocrine Clinic at Glasgow Royal Infirmary between 1963 and 1983.

Patients, Methods and Results

Evidence was sought of goitre or thyroid dysfunction occurring before or after the treatment of Cushing's syndrome. Iatrogenic secondary hypothyroidism related to pituitary surgery, or irradiation was excluded. Thirty-six patients had bilateral adrenal hyperplasia and were assumed to be pituitary dependant, and 14 had an adrenal adenoma. There were 10 male and 40 female patients, the mean age at diagnosis being 38.7 years with a range of 13–68 years. The mean period of follow-up was 7.5 years (range 2–21 years). No male patient had any clinical thyroid abnormality and therefore are not considered further.

In four female patients a clinically solitary thyroid nodule had occurred.

Patient No. 1 was 43 years old in 1963 when she presented with a left thyroid nodule. Radioiodine studies gave results borderline for thyrotoxicosis with a 24 h $^{131}$I-uptake of 53% of dose administered (normal 20–50% dose) and a 48 h total plasma iodine (TP$^{131}$I) of 0.52% dose per l and protein bound iodine (PB$^{131}$I) of 0.50% dose per l (normal < 0.30% dose/l). Thyroid scanning showed that the nodule was 'hot' on $^{131}$I-scanning and showed no suppression of radioiodine uptake over the nodule following the administration of sodium thyroxine 0.3 mg daily for two weeks. She was clinically euthyroid, but specific tests of thyroid function were not available at that time. Because of increasing size of the nodule she underwent partial thyroidectomy. Histology showed this to be a colloid adenoma. Cushing's syndrome due to an adrenal adenoma was diagnosed at follow-up 3 years later.

Patient No. 2 was 34 years old in 1970 when she was found to have a thyroid nodule 5 years after successful sub-total adrenalectomy for presumed pituitary driven Cushing's syndrome. Radioiodine scanning confirmed that uptake of isotope was confined to the palpable thyroid nodule with suppression of the surrounding thyroid tissue. The protein bound iodine (PB$^{131}$I) was 10 µg/100 ml (normal 4–8 µg/100 ml). Clinically she was euthyroid, and no specific treatment was given at that time. She became clinically thyrotoxic 5 years later at which time the serum thyroxine was 16.6 µg/100 ml (normal 6.5–12.5 µg/100 ml). She was given a therapeutic dose of radioactive iodine with a satisfactory clinical result.

Patient No. 3 was found to have right sided autonomous thyroid nodule with suppression of the remaining thyroid tissue in 1975, one year after bilateral adrenalectomy for presumed pituitary driven Cushing's syndrome. At that time the serum thyroxine was 64 nmol/l (normal 55–144 nmol/l) serum T$_3$ 2.4 nmol/l (normal
0.8–2.8 nmol/l), and the TSH was undetectable. She remained clinically euthyroid for 10 years, but in 1985 she showed some early clinical signs of thyrotoxicosis at which time her serum thyroxine was 109 nmol/l and serum T₃ 3.2 nmol/l; TSH was less than 0.8 mU/l, and there was no response of TSH to the intravenous administration of 200 μg of TRH. A decision about treatment of this patient has yet to be undertaken.

Patient No. 4 underwent unilateral adrenalectomy for an adrenal adenoma in 1981 at the age of 44 years. A clinically solitary thyroid nodule was detected 3 years later. A thyroid scan showed a diffuse pattern of isotope uptake with a suspicion of a photopenic area over the palpable nodule. Thyroid function tests showed a total T₄ of 69 nmol/l, total T₃ of 1.8 nmol/l and TSH 0.8 mU/l. Since the nodule was small and not troubling the patient, no action was taken.

In addition to these solitary thyroid nodules, one patient developed thyrotoxicosis due to presumed Graves’ disease 16 years after successful sub-total adrenalectomy. This patient was clinically thyrotoxic but had no eye signs of Graves' disease. The left lobe of the thyroid was larger than the right, but scanning showed a symmetrical diffuse pattern of isotope uptake.

Another patient developed primary hypothyroidism (T₄ 42 nmol/l and T₃ 1.9 nmol/l and TSH > 25 mU/l) one year after remission of Cushing's syndrome was induced by transphenoidal microsurgery. A single patient was noted to have a diffuse non-toxic goitre at the time of presentation of Cushing's syndrome.

**Discussion**

Thyroid disease is common in the general population (Tunbridge et al. 1977), and the observation of occasional cases of Graves' disease, primary hypothyroidism and non-toxic goitre, in such a survey is not surprising. In particular thyrotoxicosis has been found to affect as many as 19/1000–27/1000 females depending on whether only definite or probable cases are included (Tunbridge et al. 1977). The cause of thyrotoxicosis in the UK is predominantly Graves' disease and toxic multinodular goitre with a solitary autonomous toxic nodule being much more rarely found. Solitary thyroid nodules occur in 3–4% of a non-selected population (Tunbridge et al. 1977; Vander et al. 1968). However, only around 5% of such nodules are autonomous or 'hot' as judged by isotope scanning (Hamburger 1980). Thus in this survey of patients with Cushing's syndrome we have found an unexpected preponderance of 'hot' nodules. Only two of the three patients with a 'hot' nodule in this series developed clinical and biochemical features of thyrotoxicosis, the autonomous nodule in patient 1 being removed surgically, therefore not allowing any possible clinical thyrotoxicosis to develop. There is no previous description of this association in the literature. Solitary thyroid nodules occurred both in patients with an adrenal adenoma and in those with Cushing's syndrome of pituitary origin.

The association of Cushing's syndrome and thyroid neoplasms is well recognised in medullary thyroid cancer in which the thyroid tumour produces an ACTH-like peptide. The fact that Cushing's syndrome and the autonomous thyroid nodules in this series had no constant relationship in time to each other would argue against such a mechanism.

It is possible that the association of Cushing's syndrome and autonomous thyroid nodules represents an unrecognised variant of the spectrum of multiple endocrine neoplasias. Since both Cushing's syndrome and autonomous 'hot' thyroid nodules are relatively uncommon conditions, it is difficult for any one centre to present a series large enough to allow statistical analysis. Examination of accumulated data from many centres would be of great interest in establishing if this apparent association is a genuine or chance one.

**References**


Received March 20th, 1986.
Accepted June 30th, 1986.

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