Follicular carcinoma of the thyroid following radioactive iodine treatment for Graves' disease

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Summary: A 67 year old man presented with a well differentiated follicular carcinoma of the thyroid 17 years after he had been given radioactive iodine for Graves' disease. As this was insufficient to cure him he had continued to take propylthiouracil regularly. The tumour, which had completely replaced the thyroid, was apparently maintaining thyrotoxicosis. The implications of this management are discussed and it is concluded that antithyroid drugs should not be given on a long term basis after therapeutic radioiodine has been administered.

Introduction

One of the long term fears of radioiodine (¹³¹I) treatment for thyrotoxicosis has been the possibility of radiation-induced malignancy. In general it has been allayed, for in a very large co-operative study there were only 28 malignancies, nine in the first year, in 27,714 cases where ¹³¹I was the only treatment given.¹ However, most of the subjects treated in the early years were over 50 years of age and many would have died from other causes before a malignancy could have developed. Carcinoma of the thyroid has certainly occurred after a long interval following irradiation of the neck for a variety of conditions both in children and adults.²⁻⁵ In these instances it is probable that only a low dose of radiation was delivered to the thyroid. There is now an ever increasing use of ¹³¹I treatment in younger people, many being given only a low dose, so the problem requires continual observation.

Case report

A man, aged 48, was first seen in 1967 with a confirmed diagnosis of thyrotoxicosis. Treatment with carbimazole caused a rash, but he was then successfully controlled with propylthiouracil (PTU) which was continued for 18 months. When this was stopped he soon relapsed and he was then referred

for ¹³¹I treatment. On examination in 1969 he was hyperactive with a marked tremor, hot and moist hands, mild exophthalmos with lid retraction. There was a palpable small diffuse goitre but no bruit was heard. Pulse rate was 100 per minute, regular in rhythm. Investigations confirmed thyrotoxicosis, thyroid autoantibodies positive.

He was given 145 MBq (4 mCi) ¹³¹I, designed to deliver 3,500-5,000 rads⁶ and he was then put back on PTU, ultimately being controlled on 50 mg daily. This was continued for a year but when it was stopped he relapsed promptly and, unfortunately, he refused further ¹³¹I which had been in the original treatment protocol. Consequently he was put back on PTU. During the next 15 years PTU was stopped on several occasions, and he continued to refuse ¹³¹I treatment, as he felt so well on the tablets, PTU was continued, latterly 75 mg daily. In 1982 he was noted to have a firm diffuse goitre, which was slightly larger on the right.

In 1986 following a car accident he was found to have a hard diffuse goitre with recent hoarseness of voice due to a right recurrent laryngeal nerve palsy. Total thyroidectomy, which was done in two stages, revealed that the whole of the thyroid had been replaced by tumour. Histologically there was widespread infiltration by well differentiated follicular carcinoma with areas of more marked nuclear pleomorphism. Capsular invasion was evident but vascular invasion was not seen. He recovered well from the operation and he remains fit on thyroxine without any evidence of residual tumour or metastases.

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Discussion

The patient is unusual in that he required continued treatment with PTU to keep him euthyroid following an initial small dose of ^{131}I which was given 17 years before presentation with a well differentiated follicular carcinoma. He was one of a group of patients who were deliberately treated with half the conventional dose to try to lessen the incidence of hypothyroidism.^{7,8} In the protocol patients who relapsed following a year's course of an antithyroid drug were to be given further ^{131}I to effect a cure but unfortunately he refused this at the time and on several occasions subsequently. He was, in effect, a human model of Doniach's work on rats.

Doniach⁹ showed that in rats treated with methylthiouracil (MTU) alone 78% developed adenomata, none malignant; in those treated with ^{131}I alone 42% developed adenomata, none malignant. But when they were given both ^{131}I and MTU 98% developed tumour, of which 22% were malignant. He argued, probably correctly, that the MTU had this effect by chronic over-production of TSH, but there is a possibility that MTU was carcinogenic when given after irradiation.

In Graves' disease occult cancers, mainly papillary, are variously reported in 0.5–2.5% of those treated by thyroidectomy.^{10–12} The clinical potential of the occult cancers is unknown but 4 (0.3%) cancers occurred in 1,238 patients treated solely with antithyroid drugs in the co-operative survey.¹ In 100 cases of thyroid cancer referred to a radiotherapy centre 7 had co-existent hyperthyroidism¹³ and Hancock *et al.*¹⁴ reported 10 cases of co-existent carcinoma and hyperthyroidism so the problem is a real, albeit a small, one.

From Doniach's work and the incidence of occult cancers it is not surprising that the patient developed a carcinoma for he had a persistent stimulus to the thyroid, albeit a thyroid stimulating immunoglobulin rather than TSH, and he had been earlier treated with a small dose of ^{131}I . Gossage *et al.*¹⁵ have reported a somewhat similar case who developed and died from an anaplastic carcinoma 23 years after ^{131}I therapy. Burke *et al.*¹⁶ also reported a 37 year old female who developed a follicular carcinoma 11 years after ^{131}I therapy, having been mildly hyperthyroid all the time. However, persistent thyrotoxicosis has not been a feature in most other cases reported.^{1,17}

Even though this case is a rarity it suggests that it is most unwise to allow thyrotoxicosis to continue for more than a year or two after a therapeutic dose of ^{131}I . If by that time a patient is not euthyroid he should be given more ^{131}I . Presumably if sufficient ^{131}I has been given to render the patient euthyroid, most thyroid cells will have been irradiated and lost the power of replication even if some are still functioning.

This patient was also unusual in that the follicular carcinoma, which was well differentiated, had replaced virtually all of his thyroid so it must be presumed that this was not only maintaining thyroid function but also causing a persistent thyrotoxicosis. He had been attending a third hospital between 1982–1986 and it is not clear when the change over took place but it was probably a slowly progressive affair. Although a functioning thyroid cancer can very rarely cause thyrotoxicosis we have not been able to trace a similar case where it has gradually taken over in Graves' disease.

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