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CASE REPORT

Mediastinal Images Resembling Thymus Following 131-I Treatment for Thyroid Cancer

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ABSTRACT: ***Mediastinal Images Resembling Thymus Following 131-I Treatment for Thyroid Cancer. L. Montella, M. Caraglia, A. Abbruzzese, A. Soricelli, M. Caputi, G. Squame, M. Salvatore, S. Del Prete, G. Palmieri.***

The follow-up of Differentiated Thyroid Cancer conventionally includes serum thyroglobulin and periodic Whole Body Scans. The uptake of 131-I in normal and pathological tissues different from metastatic thyroid cancer sites is a cause of false-positive scans. Among them, mediastinal uptake caused by thymic hyperplasia can be observed. The aim of the present study was to review a series of 573 patients with differentiated thyroid cancer treated with 131-I after surgery between 1992 and 2003 looking above all for those with mediastinal images resembling thymus. This evaluation is presented together with some hypotheses on the relationships between thymus and thyroid. Moreover, some considerations are made on the differential diagnosis between thymus and mediastinal tumour thyroid residues.

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Keywords: Thyroid cancer, thymic hyperplasia, 131-I therapy, whole body scan.

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Introduction

Differentiated thyroid cancer (DTC) patients, especially the 10-15% at high risk of cancer-related death, should have long-term monitoring for detection of recurrence or metastasis. For patients who have had ablation of residual thyroid tissue, measurement of serum thyroglobulin (Tg) levels and radioactive iodine imaging provide highly sensitive tools for early detection. The whole-body scan following 131-I administration is obtained while serum thyrotropin (TSH) is high. The high TSH stimulates the uptake of iodine by normal and neoplastic thyroid cells as well as normal tissues able to concentrate iodine.

Salivary glands, stomach, breast [1, 2] as well as primary lung cancers and inflammatory lung diseases [3, 4] can be visualised following radioiodine administration as sites of uptake.

The uptake of 131-I in normal and pathological tissues different from metastatic thyroid cancer sites is a cause of false-positive scans.

Mediastinal uptake in patients treated with therapeutic doses of 131-I for thyroid cancer is a previously reported effect. Ramanna *et al.* [5] considered the mediastinal uptake found in 10/85 patients with differentiated thyroid cancer to be due to thyroid tissue migrated in the mediastinum or to secretions in the tracheo-bronchial tree. Accessory thyroid in the anterior mediastinum has also been described [6]. In 1979, Jackson *et al.* [7] described the uptake of radioiodine by the thymus in two patients with papillary carcinoma of the thyroid. They also demonstrated that rat thymus glands accumulate radioiodine. Thus, normal thymic cells are able to trap iodine. Several cases have then been reported describing thymic uptake of radioiodine in patients treated for thyroid cancer [8-12]. More recently, Davidson J. and McDougall R. reported seven instances of activity in the mediastinum visualised by whole body scan (WBS) among 175 patients. A mediastinal uptake was detected after administration of diagnostic doses of radioiodine in four patients, and in three cases af-

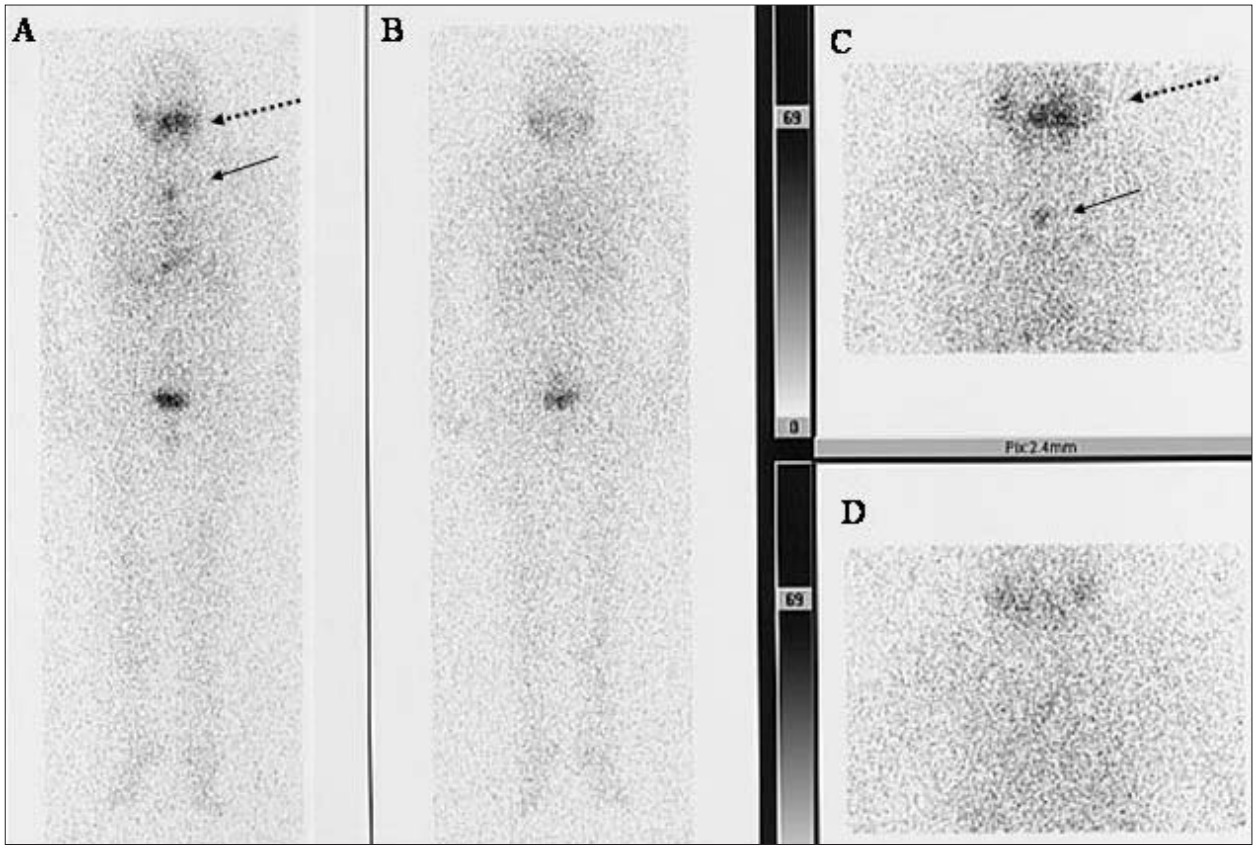

Fig. 1. - A) Anterior and B) posterior Whole Body Scan. C) Anterior and D) posterior details of mediastinum and neck. Dashed arrows show the uptake in the neck due to normal thyroid residue. Full arrows show the uptake in anterior mediastinum due to thymic hyperplasia.

Fig. 2. - Whole body PET scan showing no metabolic uptake and suggesting the presence of tumour residue.

ter therapeutic doses [13]. In the present study, we reviewed a series of 573 patients with differentiated thyroid cancer treated with 131-I after surgery between 1992 and 2003 looking in particular for those with mediastinal images resembling thymus. The revision of this large series performed induced some considerations and hypotheses on the relationships between thymus and thyroid.

Methods

We revised the records of 451 (79%) females and 122 (21%) males, ranging in age from 13 to 82 years (mean age: 47.5 years). 425 (74.2%) patients had papillary carcinoma, 128 (22.3%) had follicular carcinoma and 20 (3.5%) had Hürtle carcinoma.

After surgery, all patients underwent residual thyroid ablation with radioiodine. Post-therapy WBSs were performed 2-10 days later and patients were given suppressive therapy with L-Thyroxine. After ablation, patients underwent periodical clinical controls, including detection of Tg and antithyroglobulin antibodies (TgAbs) during treatment and after the suspension of therapy with L-Thyroxine and diagnostic WBSs.

All the scans, both diagnostic and post-treatment, were reviewed by two nuclear physicians, first separately and then together to reach a consensus.

Results

We recognised nine patients (8 females, 1 male; aged 21-39 years at entry; 7 papillary and 2 follicular thyroid carcinoma) whose post-therapy WBS showed mediastinic uptake unrelated to recurrent lymph node disease, ectopic thyroid or other possible causes determining mediastinal images. Until now they are considered disease-free. No patient received further radioiodine therapy on the basis of the observed mediastinal uptake. One of these patients, a 30 year-old girl, underwent total thyroidectomy in 1991. A papillary thyroid carcinoma was discovered. After radioiodine therapy to ablate residual thyroid tissue, the patient was submitted for a whole body scan revealing neck

and mediastinal uptake (figure 1). Positron Emission Tomography (PET) with 18-fluoro-2-deoxyglucose (FDG) was negative (figure 2) and Magnetic Resonance Imaging (MRI) confirmed thymic hyperplasia. Notably, all the patients with mediastinal uptake underwent to CT/MRI in order to confirm the presence of thymic hyperplasia and to exclude oesophageal activity. This data suggested that the uptake in the neck was due to remnants of normal thyroid tissues while the mediastinal uptake was likely determined by thymus gland. Moreover, in our series of patients, the incidence of thymic uptake after diagnostic and therapeutic administration of radioiodine was similar.

Discussion

Mediastinal images are a challenge for physicians who have to discriminate between benign and malignant uptake. A definitive pathological solution of this matter is rarely necessary because some findings can help in the differential diagnosis. A young age together with a low/undetectable thyroglobulin level, the appearance of thymus on CT scans and the functional images obtained by PET support a diagnosis of benign uptake. Thymus and thyroid appear to have some links just during embryological development. The thymus develops from the third pharyngeal pouch, migrates caudally and merges with the part located on the other side. During such migration some thymic tissue can be lost and thereafter included into the thyroid gland as isolated thymic nests. The thyroid is instead derived from the epithelium of pharynx, but some authors recognised a contribution of the fourth pharyngeal pouch. Some histological findings can be explained by such developmental mechanisms. In fact, epithelial tumors with thymus differentiation developing in the thyroid gland and in the neck have been described [14]. Moreover, ion mass spectrometry microscopy performed in one of the reported cases of radioiodine thymic uptake in thyroid carcinoma demonstrated iodine only in the thymic Hassall's bodies which have been considered similar to thyroid follicles [10]. The ability to concentrate iodide is a fundamental property of thyroid tissue, but various extra-thyroid tissues can take iodide. Human sodium iodide symporter gene is expressed in many tissues apart from thyroid. Among them, thymus has been recognised [15, 16]. Thymus uptake has been most frequently demonstrated after therapeutic rather than diagnostic doses of 131-I. Such finding implies a weaker ability to accumulate 131-I than thyroid tissue [8]. Nevertheless iodine could play an unrecognised role in thymic cell function. Thymus and thyroid exert reciprocal influences in the wide setting of neuroendocrine interactions. Thyroid hormones influence thymus physiology and stimulate thymulin secretion from the thymus [17-20]. On the other hand, thymic hormones have demonstrated activity on nervous and endocrine circuits [21, 22]. In particular, thymosin fraction 5 and homeostatic thymus hormone, two recognised secreted thymic peptides, have shown thyrotropin-inhibiting activity in young but not in old rats [21]. Thymus-pituitary axis modifies during aging, its responsiveness decreasing, but the so-called "thymopause" does not probably mean a point of no return. It was demonstrated thymic regrowth and reactivation of thymic endocrine activity by endocrinological or nutritional manipulations in old animals [23]. Exogenous thyroxine or triiodothyronine have shown these properties. Thymic size appeared significantly increased at Computed Tomography scans in untreated patients with Graves' disease [24]. Moreover, the TSH receptor was demonstrated in non-neoplastic thymic tissue and was proposed as a key factor in inducing autoimmune reactions leading to Graves' disease [24]. If use of anti-thyroid drugs is associated with decrease in thymic size [24], we cannot exclude that therapy with exogenous thyroid hormones could rescue the activity also of human dormant thymus tissue inducing, especially in more responsive younger patients, the scintigraphic appearance of iodine thymic uptake. This hypothesis is on line with previous evidence concerning active thymic function in adults [25, 26]. Many studies support the emerging notion and the clinical relevance of continuous thymic activity beyond the adulthood [27]. Apparent induction of thymic regeneration was recently reported in an adult volunteer following administration of growth hormone [24). A systemic stress can induce changes in thymic size [29]. Chemotherapy is a well-described factor determining thymic hyperplasia in a high percentage of young cancer patients [29, 30]. Similarly, after the exclusion of abnormalities related to residual disease, we can suppose that functional changes might have taken place leading to the thymic uptake visualised by radioiodine scintigraphy. Apart from the interest in differential diagnosis, this image may be consistent with a changed thymic function. Moreover, the relevance of thymus activity on the survival and responsiveness to therapy of cancer patients is still under investigation. Studies involving thymus output and peripheral T cell pool prior to and after radioiodine therapy could provide proof of effective thymus regeneration.

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