The human sodium-iodine symporter (NIS) as a key for specific thymic iodine-131 uptake

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In the last issue (pp 425–430) of the *European Journal of Nuclear Medicine* Davidson and McDougall reported a retrospective analysis of 526 diagnostic or post-treatment iodine-131 scans in 175 patients with thyroid cancer focussed on mediastinal ^{131}I accumulation attributable to the thymus. Uptake in the mediastinum was noted in 4 of 326 (1.2%) diagnostic scans and in 2 of 200 (1%) therapeutic scans.

Knowledge of false-positive findings in the diagnostic or post-treatment ^{131}I scan in patients with differentiated thyroid cancer is indispensable if unnecessary therapeutic procedures are to be avoided. False-positive findings in the chest may be attributable either to body secretions and pathological transudates or to inflammatory processes, neoplasms of non-thyroidal origin or ectopic thyroid tissue [1–10].

Thymic uptake of ^{131}I is known to be one condition which can be confused with metastatic mediastinal spread, and it has appeared to be relatively frequent (4.5%–8.2%) in small series and some case reports published previously. In these publications thymic uptake was usually described as either focal (arrowheaded or dumb-bell shaped) or diffuse [11–17]. In some patients mediastinal uptake disappeared on scans following surgical removal of normal or hyperplastic thymic tissue. It seemed reasonable to hypothesis that thymic uptake could be explained by thyroid tissue that had migrated into the mediastinum during embryogenesis, but neither ectopic nor metastatic thyroid tissue could be found in the histological specimens of these thymic glands [13, 14]. In one case accumulation of ^{131}I could be detected in the thymus by autoradiography without any evidence of tumour involvement [12], and Vermiglio et al. reported that thymic accumulation of ^{131}I was located selectively in cystic Hassall's bodies in one patient, suggesting that there may be a specific thymic uptake mechanism [16].

Recently the human Na^+/I^- symporter (hNIS), which is responsible for iodine uptake in the thyroid gland, has been cloned and characterised [18] . This transporter is located on the basolateral membrane of the thyroid follicular cells and iodine transport is made possible by an energy (Na^+/K^+-ATPase) dependent co-transport mechanism that is driven by an inwardly directed Na^+ gradient. Under physiological conditions the expression of NIS is mainly dependent on TSH and modulated by cytokines such as TNF or TGF-β1 [19]. In earlier studies it was well recognised that the thyroid gland is not the only organ that may concentrate iodine [20], and therefore it was not surprising that hNIS gene expression could be demonstrated not only in the thyroid gland but also in other tissues such as the parotid and submandibular glands, pituitary gland, pancreas, testis, mammary gland, gastric mucosa and thymus [21]. In this respect thymic expression of the NIS offers for the first time an explanation for ^{131}I uptake at a molecular level. Compared with the thyroid gland, the capacity to transport and concentrate iodide has been found to be diminished in extrathyroidal tissues, which may explain why late scanning, higher activities, and absence of remnant thyroid tissue and metastatic spread (and therefore absence of tissue with higher hNIS expression than the thymus) increase the probability that thymic tissue will be visualised after administration of radioiodine [13, 16, 22].

Michigishi et al. [13] proposed valid criteria to separate malignant from benign mediastinal uptake. Thymic uptake that becomes more prominent with repeated ^{131}I treatment, visualised only by higher activities on post-treatment scans, low serum hTg levels, younger age and a hyperplastic thymus are indicative of non-metastatic tracer uptake. It should be mentioned that beside thymic uptake, ^{131}I accumulation in the midline of the thorax may represent various conditions, e.g. tracer retention in the oesophagus, reflux of radioactive gastric fluid into the oesophagus and aspiration of radioactive saliva in the tracheobronchial tree [4, 5, 10]. Although linear uptake in continuity with the stomach is highly suggestive of oesophageal activity, focal oesophageal retention may occur and be indistinguishable from focal thymic uptake.

In 1998 Wilson et al. published retrospective data on a small number of consecutive patients in the *European Journal of Nuclear Medicine*, indicating that possible thymic uptake could be recognised in 10/38 (26%) patients. Mediastinal accumulation of ^{131}I was mainly diffuse and could be detected in eight of ten patients (80%) only on late (7-day) scans. All patients with mediastinal

accumulation of ^{131}I attributable to the thymus were of younger (<50 years) age [22]. This high prevalence of thymic uptake was somewhat surprising for us and not concordant with our own experience. In our department possible thymic uptake is a rare observation and occurs in less than 1% of post-therapy scans. Following the guidelines of the German Society of Nuclear Medicine [23], we usually do not perform scans later than 72 h following diagnostic or therapeutic application of ^{131}I, which may be one reason for the discrepancy between Wilson's data and our observations.

The publication by Davidson and McDougall in this issue of the *European Journal of Nuclear Medicine* dealing with the topic of thymic ^{131}I uptake is the first report on findings in a sufficiently large group of patients. Therefore this publication may come closer to establishing the real prevalence of thymic ^{131}I uptake than previous studies, although the authors lack correlative imaging data and histological evidence in their patients. The authors note that some of their patients with mediastinal accumulation of the tracer were detected by diagnostic imaging which was performed 66–72 h after administration of 74 MBq ^{131}I, indicating that high activities and late scanning are not prerequisites for the detection of thymic uptake.

In conclusion, thymic uptake of ^{131}I is rare, and if it does occur it will not cause major problems if the clinician is aware of the possibility of such a finding. Normal hTg values in hypothyroidism, the absence of liver uptake on the post-therapy scan and chromatographic absence of radioactive L-T3 and L-T4 make mediastinal metastasis unlikely. Correlative MRI/CT imaging and scintigraphy with ^{201}Tl or ^{99m}Tc-MIBI may be used to overcome diagnostic uncertainties in the few remaining cases.

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