Iodine-131 Uptake in Inflammatory Lung Disease: A Potential Pitfall in Treatment of Thyroid Carcinoma

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A mixed differentiated thyroid carcinoma was found in a small asymptomatic nodule in a 44-yr-old woman with recurrent chest infections and bronchiectasis. After total thyroidectomy and 162 mCi (6 GBq) radioiodine ablation there was uptake in the thyroid remnant and in both lungs, interpreted as lung metastases. In 2 years she received further three 162 mCi (6 GBq) doses of ^{131}I, as scans showed very similar lung activity. Another scan, during thyroxin suppression, showed again activity in the lungs. A 47-yr-old male patient with similar respiratory disease and no history of thyroid disorder volunteered to undergo radioiodine scan while on triiodothyronine suppression. His scan, too, showed concentration in the lungs. The female patient died 7 years after the diagnosis of lung thyroid metastases was made. No metastasis was found at autopsy. Radioiodine lung uptake may occur in patients with chronic inflammatory lung disease, presenting a potential diagnostic pitfall in patients with differentiated thyroid carcinoma.

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Between 10% and 40% of adult patients with differentiated locally invasive thyroid carcinoma develop distant metastases, usually to the lung, which may accumulate radioiodine even in the presence of a functioning thyroid remnant (*1*). A case of a female patient with serendipitously diagnosed thyroid carcinoma is described. After surgical and radioiodine ablation lung concentration of iodine-131 (^{131}I) was interpreted as lung metastases, but the subsequent course has excluded this diagnosis.

CASE REPORT

A white female patient, born in England in 1936, was referred to the Respiratory and Nuclear Medicine Departments of the Prince of Wales Hospital after she moved to its geographical area in May 1983, complaining of productive cough, modest reduction in exercise tolerance and anxiety regarding her lung condition. She had whooping cough in infancy and possibly asthma and transient pulmonary infiltrates in childhood and early adult life. In 1967 and 1969 she was treated for pulmonary tuberculosis with streptomycin, PAS and INAH for a total of 30 mo; no positive bacteriology was obtained. She remained well until 1976 when she started to have intermittent cough, sometimes with purulent sputum.

After migrating to Australia in 1978 investigations including x-rays, tomography and bronchography showed evidence of bilateral upper lobe bronchiectasis, in retrospect consistent with the sequelae of allergic bronchopulmonary aspergillosis. Further courses of antituberculous therapy, including rifampicin, isoniazid and ethambutol, were given on account of positive sputum smears for acid fast bacilli, subsequently identified as *M. Kansasii*. In 1980, the plain chest radiograph showed thickening of bronchial walls and bronchiectatic changes (Fig. 1).

In 1980, on a routine medical examination, an asymptomatic nodule 1 cm in diameter was discovered in the right lobe of the thyroid gland, shown as nonfunctioning in the pertechnetate thyroid scan. Biopsy revealed infiltrating mixed papillary/follicular thyroid carcinoma. A total thyroidectomy was performed, followed 4 wk later by an ablative dose of 162 mCi (6 GBq) of ^{131}I. Three days later a whole-body scan demonstrated uptake in the thyroid remnants and in the lungs (Fig. 2A), interpreted as lung metastases. Three more 162 mCi (6 GBq) doses of radioiodine were administered 6, 13, and 23

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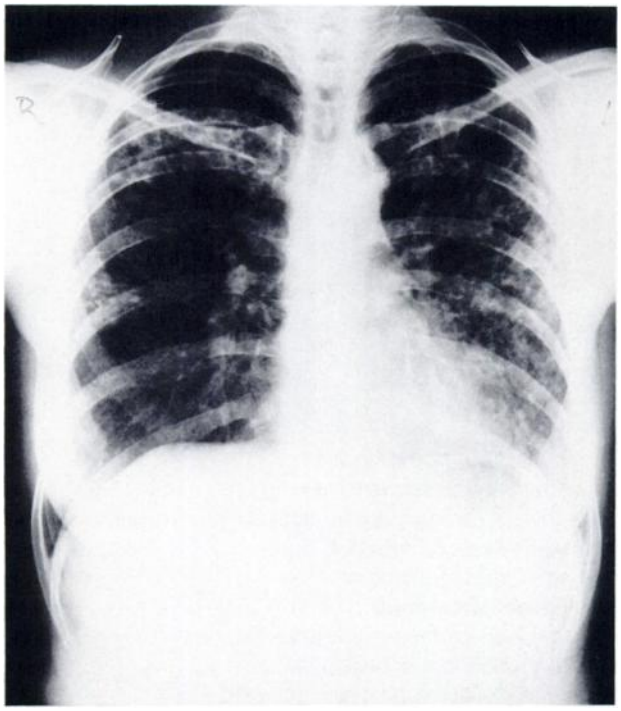

FIGURE 1
The plain chest radiograph of the patient with thyroid carcinoma at the time this diagnosis was made (1980) showed diffuse thickening of bronchial walls, more marked in the upper zones where there were also apical bullae.

mo after the initial ablation. After each dose whole-body scans showed no uptake in the neck, but a similar pulmonary concentration to that observed in the scan after the initial radioiodine ablation persisted (Fig. 2B, 2C).

Serum thyroglobulin was assayed on five occasions after the initial surgical and radioiodine ablation, during thyroid suppression, as well as during hypothyroid periods prior to scans, and was always below detection limits.

In 1983, when first seen in our clinics she had persistent cough with intermittently purulent sputum. There were widespread bilateral rales which persisted throughout her subsequent course. Chest radiographs showed no significant change in comparison with the 1980 films apart from transient increase in sputum retention (Fig. 3). The radiographs lacked the characteristic appearances of lung metastases, although radiologically this diagnosis could not be ruled out.

There was a mildly positive skin test to aspergillus but precipitins were negative; no fungal elements were seen in the sputum nor were fungi isolated. M. Kansasii was consistently isolated from sputum. A Mantoux test 1:1000 OT was positive (20 mm).

In 1983, on review of the course of her thyroid disease and unvarying scan and radiographic appearances (Figs. 1, 2A–2C, and 3), the possibility of a nonspecific uptake of radioiodine in the lungs was considered. Such an uptake should be governed by mechanisms different from thyroid iodine trapping and hence would not be affected by thyroxin suppression. The patient agreed to have a radioiodine scan during thyroxin suppression (200 μg daily). On this dose her serum TSH was not measurable. Fifty-four millicuries (2 GBq) of ^{131}I were used for this scan with images obtained at 48 and 120 hr. These showed lung uptake of similar intensity to that observed after the previous four therapeutic doses of radioiodine (Fig. 4).

Although this result supported our hypothesis, differentiated lung metastases may occasionally accumulate radioiodine even in the presence of functioning thyroid tissue. Were this the case in our patient withdrawal of further radioiodine might have denied her potentially lifesaving therapy. In view of the desirability to prove that nonspecific lung uptake may occur in patients with chronic lung disease, the medical dilemma was explained to a 47-yr-old male patient with a similar respiratory illness but no history of thyroid disease.

This patient had progressive cough with purulent sputum since his late twenties. On several occasions in the preceding year he had been admitted with respiratory failure with carbon dioxide retention, and twice with frank right heart failure. His pulmonary function tests indicated severe airways disease. His chest radiograph showed bronchiectatic changes, confirmed by tomography, involving the whole of the right lung and the left lower zone (Fig. 5). Supportive evidence for a diagnosis of mucoviscidosis was provided by duodenal aspiration.

The "control" male patient volunteered to have a radioiodine scan, provided that the radiation dose to his thyroid gland was minimized. To achieve this the scan was performed after 3 wk pretreatment with 80 μg of triiodothyronine per day, using 54 mCi (2 GBq) of ^{131}I. This scan showed a very high concentration of radioiodine in both lung fields (Fig. 6). Three years later the patient remains euthyroid, with normal levels of thyroid hormones, no palpable thyroid abnormality and no need for thyroid replacement therapy.

No further radioiodine therapy or scans were given to our patient with thyroid carcinoma.

Respiratory condition of our female patient remained reasonably stable with occasional fluctuating pulmonary infiltrates attributed to sputum retention. In 1985, her exercise tolerance worsened and she developed anemia (hemoglobin 8.7 g), considered after investigation to be due to chronic infection. Numerous acid-fast bacilli were in all sputum smears and M. Kansasii continued to be cultured. In 1986, bilateral cavitation or bullous change developed in chest radiographs, and she was then commenced upon ansamycin, ethambutol and INAH. This produced transient clinical and bacteriologic improvement over the next 10 mo but following an acute respiratory illness she developed hypoxemia and carbon dioxide retention, and died in February 1987. Autopsy showed bilateral peribronchial fibrosis with bronchiectasis in the upper lobes, and cavitating tuberculosis with typical tubercles containing acid-fast bacilli. There was neither macroscopic nor microscopic evidence of lung metastases.

DISCUSSION

Prognosis of patients with treated differentiated thyroid carcinoma is generally very favorable. However, in ~10–40% of adult patients, locally invasive differentiated thyroid carcinoma may be complicated by distant metastases, frequently to the lungs (*1–3*), although some authors have reported a lower incidence in adults (*4–5*). Pulmonary metastases are usually functional. Occasionally their hormonogenesis may suffice to

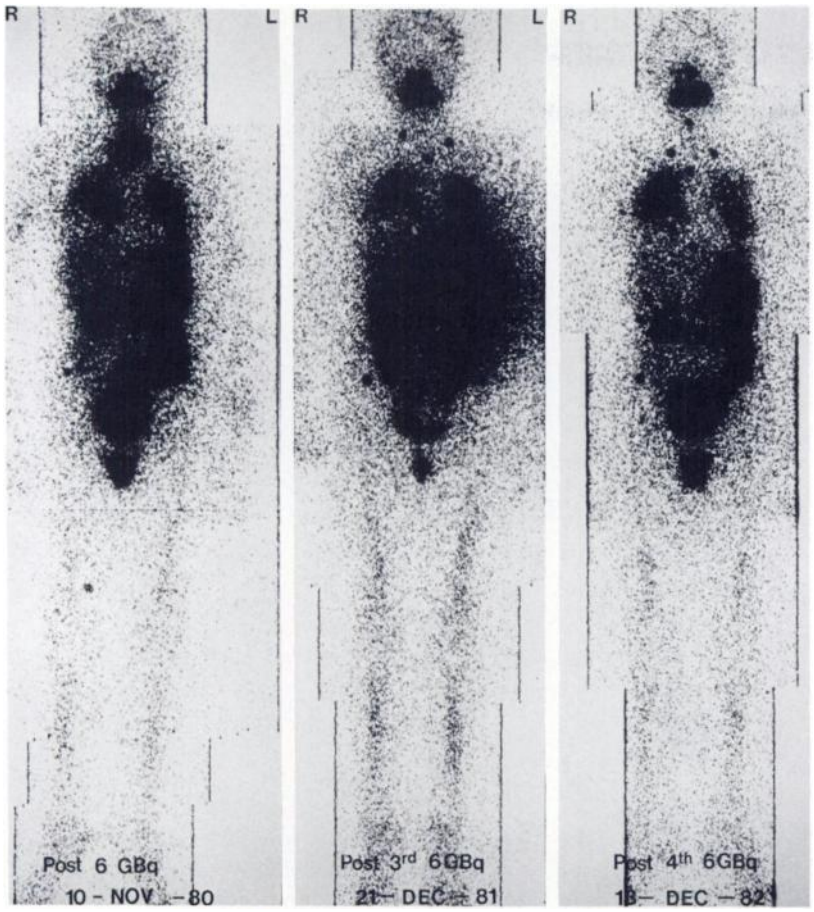

FIGURE 2
Whole-body scans performed after ablative doses of radioiodine. Left: after the first dose, November 1980; Center: after the third dose, December 1981; Right: after the fourth dose, December 1982. Isotopic markers indicate the chin, both ends of the thyroidectomy scar, sternum and both iliac crests.

maintain euthyroidism in patients after thyroid ablation without thyroid hormone replacement (*6*), or may take up radioiodine even in the presence of a functioning thyroid remnant (*1*). More commonly, however, uptake of radioiodine can be detected by scanning only after a period of iatrogenic hypothyroidism with resulting endogenous TSH stimulation. Some lesions with radioiodine uptake too low to permit scintigraphic visualization after a relatively small scanning dose may be seen after the administration of a large therapy dose (*7–9*).

Our patient had definite pulmonary concentration of radioiodine after the first ablative dose of ^{131}I, in the presence of a functioning thyroid remnant. This pulmonary uptake was understandably regarded as diagnostic of lung metastases. Neither the absence of typical changes in the chest radiographs nor the relatively small size of the primary tumor and lack of lymph node metastases excluded the possibility of metastases in view of the histologic evidence of invasion of the capsule, the patient's age, and the fact that pulmonary radioiodine uptake may precede radiological changes (*2*).

Between October 1980 and December 1982 the patient received a cumulative dose of 670 mCi (24.8 GBq) of radioiodine from four scanning doses (5.4 mCi, 200 MBq each) and four therapy doses (162 mCi, 6 GBq each), but the only difference between all the post-therapy scans was the disappearance of the thyroid remnant after the first ablative dose, the lung uptake remaining unchanged. There was no evidence of other metastases or of a local recurrence. Her serum TSH (during thyroid replacement) and serum thyroglobulin (on as well as off thyroxine medication) were below the limits of detection. The possibility of an alternative mechanism for radioiodine concentration in the lungs was therefore considered. The chest physician had independently taken the view that the natural history and the chest radiographs over 3 years indicated no basis for the diagnosis of metastases.

It is well known that inorganic iodine salts have been traditional ingredients of cough mixtures for over 100 years. It was believed that these salts increased the volume of mucus (expectorant action), and reduced its consistency (mucolytic action) (*10–11*). The mechanisms of these actions are not understood. Richardson et al. (*10*) suggested that possibly iodide salts may be secreted into the airway against a concentration gradient and the osmotic pressure exerted by the iodide ion may increase mucus volume. For a clinically significant expectorant effect, relatively high doses of iodide salts are required, far in excess of the equivalent weight of the administered radioiodine. However, it can be expected that ingested radioiodine salt would mimic

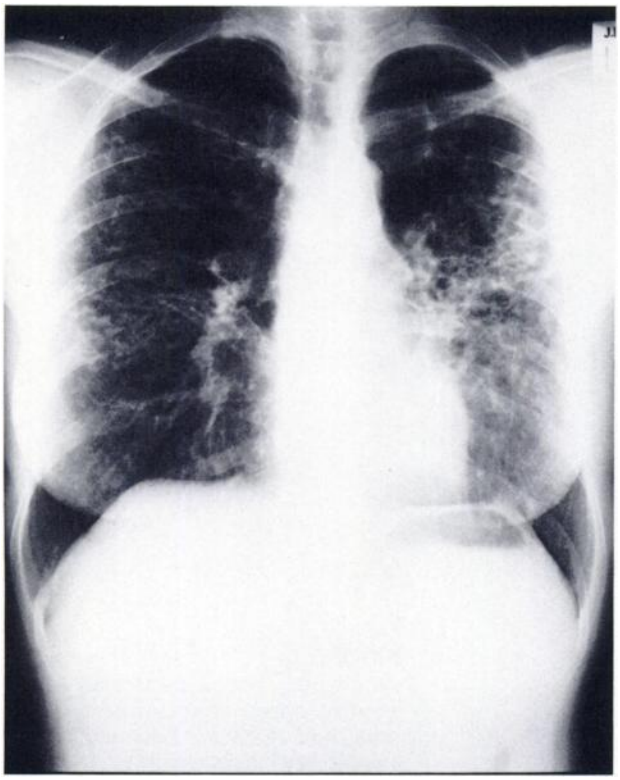

FIGURE 3
The plain chest radiograph of 1983 showed similar changes as in 1980 (Fig. 1), with some (transient) sputum retention.

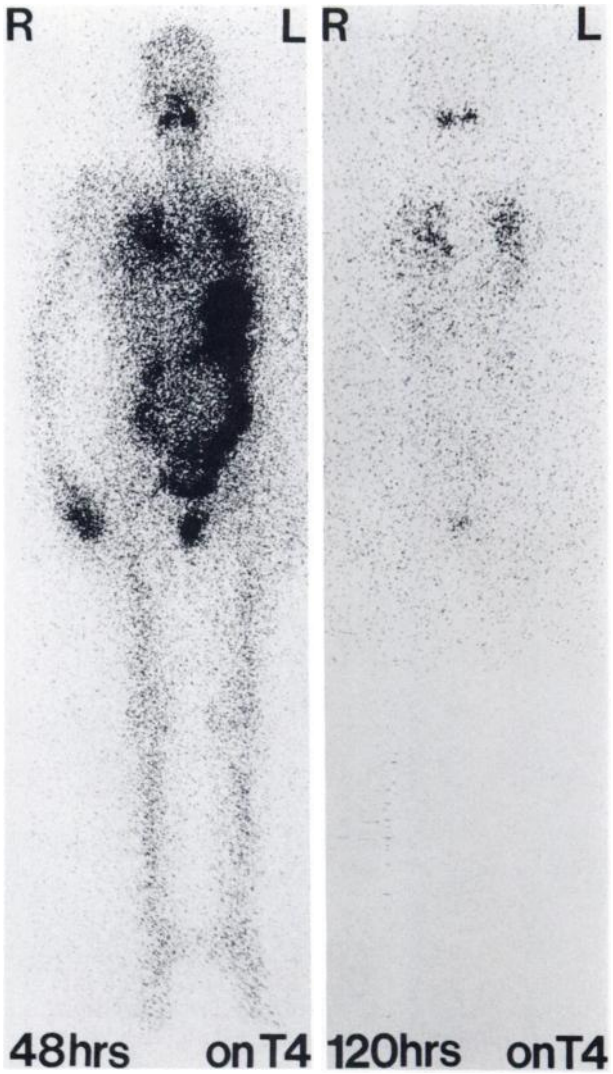

FIGURE 4
Whole-body radioiodine scan obtained during thyroxine replacement therapy in 1983. Note activity in the right hand in a handkerchief patient used during her bouts of cough.

the distribution pattern of pharmacologic doses of stable iodide salts. The pattern of such distribution should be detected by scintigraphy, especially if high doses of radioiodine are administered.

It is not known whether bronchial concentration of iodide is higher in chronic airways disease than in normal subjects. Certainly in thyroid carcinoma patients with a healthy respiratory tract no lung uptake is seen in the scans after large therapy doses of radioiodine. Whereas this indicates the absence of accumulation in normal bronchi, the concentration of iodide salts might be higher in patients with bronchopulmonary disease, simply due to hyperemia of the inflamed mucosa, notwithstanding the mechanisms suggested by Richardson et al. (*10*). There is no evidence in the literature to suspect variations in the pharmacokinetics of iodide salts in cough mixtures related to the thyroid status. On the other hand suppression of endogenous TSH leads to suppression of radioiodine uptake by thyroid metastases.

Persistence of lung uptake of radioiodine during thyroid suppression would therefore favor nonspecific concentration in chronically inflamed lung tissue rather than in lung metastases from thyroid carcinoma. The informed consent was therefore obtained for administration of radioiodine during thyroxin suppression. A 2-GBq dose was chosen to obtain scans of sufficient photon density, permitting comparison with the previous scans performed after 162 mCi (6 GBq) doses. Furthermore radioiodine scan was also performed in another patient with similarly severe bronchiectasis, with comparable length of symptoms and no history of thyroid disease.

Like the reported female patient with thyroid carcinoma this man was highly intelligent, fully informed and knowledgeable about his condition and thus more than usually competent to give consent to any investigative procedures. The "control" patient was invited to consult with a senior consultant physician to the hospital and with his own general practitioner, to both of whom the proposed procedures were fully explained. Both patients denied intake of any iodine preparations. Both at various times had theophylline, sympathomimetic agents as an aerosol and conventional antibi-

FIGURE 5
The plain chest radiograph of the "control" patient showed marked thickening of bronchial walls and bronchiectatic changes through the whole of the right lung and in the left lower zone.

FIGURE 6
Radioiodine scan of the "control" patient with severe bronchopulmonary disease and no history of thyroid disease during triiodothyronine suppression (see text). Note activity in the lungs, but some thyroid uptake was evident in spite of T_3 suppression.

otics. These patients were strikingly similar—they were relatively young, they had diffuse bronchial abnormality, they had more or less persistent respiratory infection and some airway obstruction.

Positive lung uptake in the "control" patient further supports our hypothesis of the nonspecific nature of such uptake in patients with chronic inflammatory lung disease.

In the subsequent 4 years our patient was not given any further radioiodine scans or therapy and did not develop any clinical or radiological evidence of lung metastases, her serum thyroglobulin remained below detection limits, and at autopsy there was neither macroscopic nor microscopic evidence of lung metastases.

In the terminal 2 years our patient suffered from anemia and pulmonary fibrosis was found at autopsy. This could be explained by the chronic inflammatory lung disease and chronic infections. To what extent this process was influenced by the radiation dose she received 3–5 yr earlier remains speculative.

The "control" patient remains euthyroid, has normal levels of thyroid hormones, no goiter, and does not require thyroid replacement.

We suggest that radioiodine uptake in the lungs of these two patients was nonspecific, related to their chronic severe inflammatory lung disease, and was not due to pulmonary metastases. The only reference to similar pulmonary iodine concentration found in the literature is in a footnote of an article by Echenique et al. (*12*), describing equivocal pulmonary uptake, first thought to be due to metastases, but subsequently attributed to pulmonary fungal infection.

Uptake in the lungs of thyroid carcinoma patients with chronic infections of the respiratory tract should therefore be interpreted with caution as it may not represent metastatic disease and may lead to unnecessary doses of radioiodine.

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REFERENCES

1. Beierwaltes WB. The treatment of thyroid carcinoma with radioactive iodine. *Semin Nucl Med* 1978; 8:79–94.
2. Turner JE, Weier GL, Jr. Pulmonary metastases from

thyroid carcinoma detectable only by I-131 scan: treatment and response. *J Nucl Med* 1972; 13:852–855.
3. Harness JK, Thompson NW, Sisson JC, et al. Differentiated thyroid carcinoma—treatment of distant metastases. *Arch Surg* 1974; 410–419.
4. Crile G, Jr. Changing end results in patients with papillary carcinoma of the thyroid. *Surg Gynec Obstet* 1971; 132:460–468.
5. Mazzaferri EL, Young RL, Oertel JE, et al. Papillary thyroid carcinoma: the impact on therapy in 576 patients. *Medicine* 1977; 56:171–196.
6. DeGroot LJ, Stanbury JB. The thyroid and its diseases, New York: J. Wiley & Sons, 1975:696.
7. Preisman RA, Halpern S. Detection of metastatic thyroid carcinoma after the administration of a therapeutic dose of 131-iodine. *Eur J Nucl Med* 1978; 3:69–70.
8. Ng Tang Fui S, Maisey MN. Thyroid disease. In: Maisey MN, Britton KE, Gilday DL, Eds. *Clinical nuclear medicine.* London: Chapman and Hall, 1983:221.
9. Coakley AJ, Page CJ, Croft D. Scanning dose and detection of thyroid metastases. *J Nucl Med* 1980; 21:803.
10. Richardson PS, Phipps RJ. Tracheobronchial mucus secretion. In: Widdicombe J, Ed. *International encyclopedia of pharmacology and therapeutics, Section 104: respiratory pharmacology.* Oxford: Pergamon Press, 1981:462.
11. Hexheimer H. Sudden death in a young asthmatic [Letter to editor]. *Br Med J* 1969; ii:246.
12. Echenique RL, Kasi L, Haynie TP, et al. Critical evaluation of serum thyroglobulin levels and I-131 scans in post-therapy patients with differentiated thyroid carcinoma: concise communication. *J Nucl Med* 1982; 23:235–240.