Unusual Fatal Effect of Radioiodine (I-131) Therapy : A case report

Mathonnet M[1], Clavel M[2], Labrousse F[3], Chianéa T[4]

[1]Departments of Digestive and Endocrine Surgery, [2]Medical-Surgical Intensive Care Unit, [3]Pathology, and [4]Clinical Biology. Dupuytren Teaching Hospital, 2 avenue Martin Luther King, 87042 Limoges, France

Abstract

The aim of radioiodine therapy following surgery for thyroid carcinoma is to ablate the remnant thyroid tissue in the neck by delivering a minimum dose of 300 gray to the residual thyroid tissue. Side-effects are usually minimal and transient, and use of rhTSH can reduce their incidence. In patients with functioning metastases, successive doses of radio iodine are administered until complete ablation of metastatic disease is achieved. A 54-year-old woman with diffuse pulmonary metastases from thyroid cancer died from a fatal sudden alveolar haemorrhage that occurred 3 weeks after radioiodine therapy. Post mortem biopsy of specimens taken from the sites of pulmonary metastasis revealed massive haemorrhage and apoptosis. It is known that in vitro, beta-irradiation can activate apoptosis pathways. This effect seems to depend on dose of radioiodine and time point. In humans, I-131 therapy can induce apoptosis in hyper-functioning thyroid tissue. This effect is dependent on iodine concentration which is dependent on NIS expression itself. A sudden wave of apoptosis occurring 3 weeks after radioiodine dose could be lethal. On the other hand in order to have favourable treatment response it is essential to have high I-131 uptake by pulmonary metastases. Although fatal effect of radioiodine therapy are rare, this particular case suggests that a high level of I-131 concentration in critical organs detected by post-therapy whole-body scan (WBS) should be an indication for imposing particular care in the management of such patients, and perhaps consideration for prolonged hospitalization and late discharge.

Key words: radioiodine, side-effect, thyroid carcinoma, apoptosis, alveolar haemorrhage.

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Correspondance :
M Mathonnet, MD, PhD
Department of Digestive and Endocrine Surgery
Dupuytren Teaching Hospital
2 avenue Martin Luther King
87042 – Limoges – France
Email : mathonnet@unilim.fr

Introduction

Radioiodine therapy in patients with differentiated decreases the recurrence and mortality rates by eradicating microscopic residual postoperative foci. In patients with functioning metastases, successive doses of radio iodine are administered until complete ablation of metastatic disease is achieved. Whole-body scans performed 3-7 days after I-131 administration facilitates the detection of recurrence or functioning metastasis. Complete responses to I-131 therapy have been observed in 33-50% of patients with distant metastasis that take-up I-131(1). Even if side effects of radioiodine are usually minimal and transient, its adverse effects could exceed the eventual benefits, particularly in low-risk patients. Rosario (2) had confirmed in a prospective investigation that a preparation with recombinant human thyroid-stimulating hormone lowers the adverse effects without compromising the efficacy of treatment. We observed an uncommon fatal side effect occurring after a usual routine radioiodine administration.

Case Report

A 54-year-old woman was referred to the endocrine surgeon for a 3 cm nodule of the right lobe of the thyroid, known since 9 years. A fine needle aspiration biopsy of the nodule was performed, which revealed suspicious thyroid cells, but the patient did not want to undergo surgery. The nodule increased and became painful and lymph nodes became palpable in the central neck compartment. Neck ultrasonography showed that the thyroid nodule was solid, hypoechogenic, irregular; there were sub-centimetre nodules in the left lobe and suspicious lymph nodes in the central and ipsilateral neck compartments. A total thyroidectomy with a dissection of the central and ipsilateral neck compartments was performed. The central compartment was grossly involved by bulky lymph node metastases but the recurrent laryngeal nerves and the upper parathyroid glands could be preserved. She had no surgical complication and was discharged on day 4. Histology revealed that the 3-cm nodule was a non-encapsulated follicular variant of papillary carcinoma, and that a sub centimetre papillary carcinoma lain in the isthmus. Sixteen nodes were removed from the central compartments, 15/16 were invaded. Radioiodine therapy was given 4 weeks later. On admission, the patient was clinically hypothyroid; serum TSH and serum Tg were 100 µUI/ml and 214 ng/ml respectively with negative anti-Tg auto-antibodies and a normal recovery test. A therapeutic activity (100 mCi, 3700

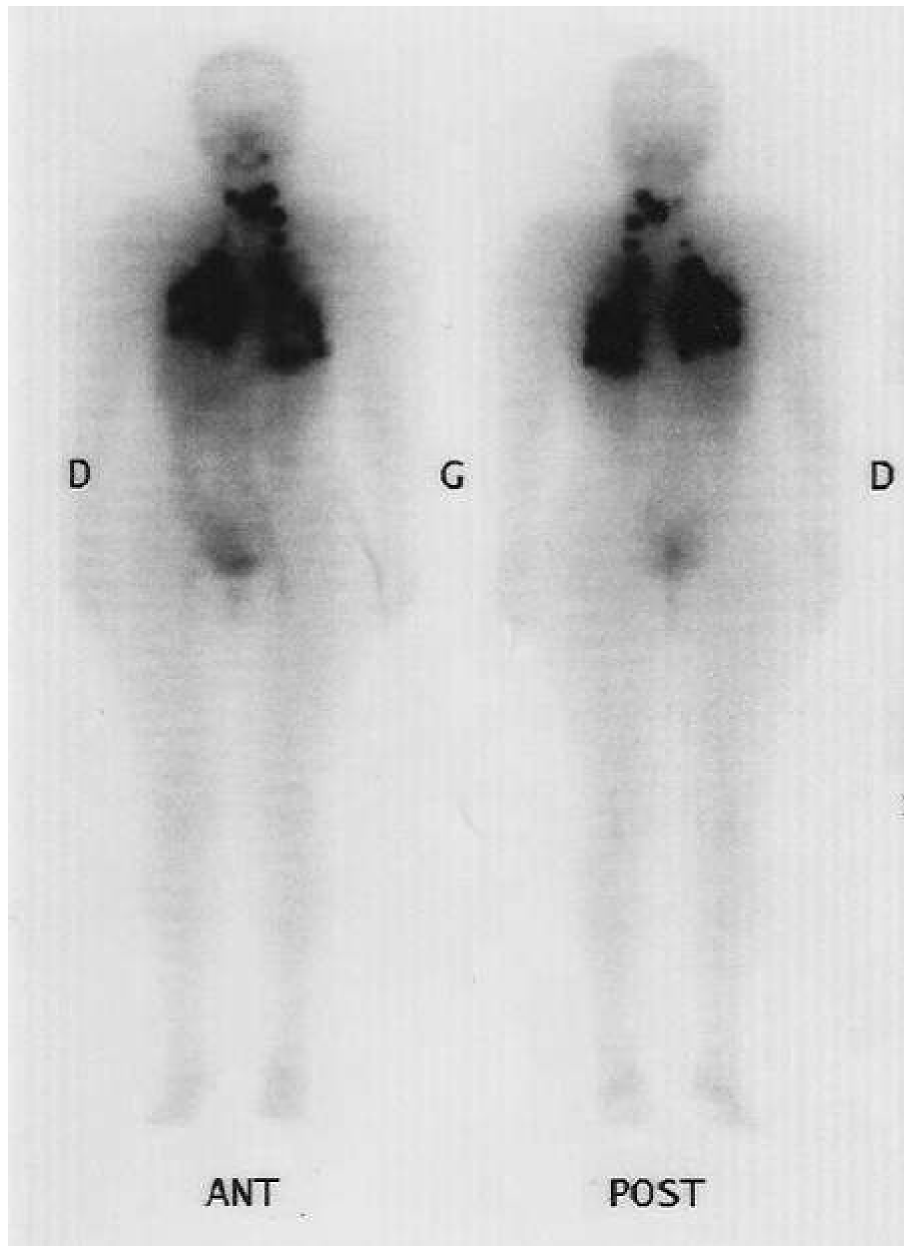

Figure 1 : Post-therapy Whole body scan performed 5 days after radioiodine shows I-131 concentration in remnant thyroid, cervical nodal and bilateral lung metastases.

Mbq) of Iodine-131(I-131) was administered without any diagnostic scan before. A post-therapy WBS was performed 5 days after the ablative treatment, which revealed a small volume of remnant thyroid tissue in the neck and functioning metastases in cervical lymph nodes as well as in bilateral lungs. The pulmonary metastases were very extensive, exhibiting intense I-131 uptake. These were detected by WBS alone (Figure 1). Subsequent to I-131 therapy, the patient was placed on Levothyroxin (LT4) at a daily dose of 150 µg orally and discharged from the hospital after scheduling a second I-131 dose (150 mCi) after 6 months.

However, three weeks after the first dose of I-131 the patient suffered from cardiac arrest in her bath. During cardio pulmonary resuscitation procedure, a large and unexpected quantity of blood was aspirated through the endotracheal tube. After fifteen minutes of resuscitation, the patient recovered. The Electrocardiogram, cardiac ultrasonography and coronary angiography procedures were normal; no reasonable cause could be identified to explain this cardiac arrest and alveolar haemorrhage. A routine X-Ray of the chest revealed diffuse opacities in the upper lobe of the left lung were, and several centimetric pulmonary noodles and diffuse alveolar opacities were noted on CT scan. Bronchoscopy revealed blood that covered all the bronchial divisions. In spite of controlled hypothermia to prevent cerebral damage, anoxia was soon evident and the patient died seven days later with an advanced directive to withhold life-sustaining treatment. The main diagnosis was hypoxemia secondary to alveolar haemorrhage, which led to the cardiac arrest. Histological examination of the post-mortem pulmonary biopsies

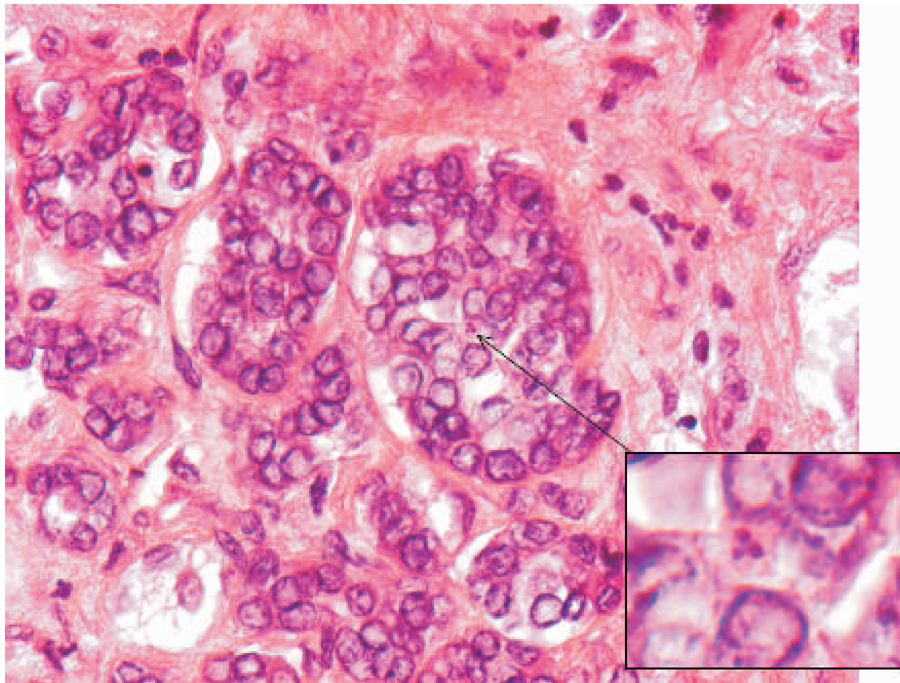

Figure 2 : Post mortem pulmonary biopsies show features of pulmonary metastases from a papillary thyroid carcinoma in a follicular variant with typical "ground glass" nuclei. There is no necrosis. Apoptotic cells with an eosinophilic cytoplasm and dense nuclear chromatin fragments could be visualized (arrow).

revealed pulmonary metastases of a well-differentiated papillary carcinoma in a follicular variant. There was no necrosis, but apoptotic cells could be detected.

Discussion

As far as we know, this is the first case concerning a fatal outcome of iodine-131 therapy for pulmonary metastasis of well-differentiated thyroid carcinoma. Radioactive iodine is widely used in the treatment of metastatic well-differentiated thyroid carcinoma. Its side effects are usually transient and mild. The most frequently encountered symptoms include gastric pain, nausea, vomiting, and acute sialadenitis which occur in 60-80% of patients and last a few days (2,3). Blood and bone marrow complications are unusual. Studies of large cohorts of patients treated with I-131 have demonstrated a significant increase in the risk of leukaemia and solid tumours, such as breast or bladder carcinomas (2). The risk increases by increasing cumulative doses, and by reducing the intervals between each doses. The pulmonary complications seem rare, and to be particularly prone in children (4). Pulmonary fibrosis is developed in patients treated repeatedly for extensive pulmonary metastases of the macronodular variety or when extensive interstitial disease is present (4). However, radiation fibrosis is now uncommon and could be avoided by administering limited doses of I-131 with intervals of several months between treatments (5).

The present clinical case most likely indicates, for the first time, a sudden haemorrhage in pulmonary metastasis, occurred 21 days after the first radioiodine intake and responsible of a fatal anoxia. Acute haemorrhages are unlikely. Holmquest reported a similar fact in brain metastasis of a papillary thyroid carcinoma (6), but Ronga have never noticed fatal effect of radioiodine on patients with lung metastasis over his forty years' experience (7).

Most of the radiation dose from I-131 is delivered by beta-particles. Gamma radiation contributes only 10% of the total radiation dose. Ninety percent of the energy of beta particles is absorbed within 0,8 mm from the source, and large doses of I-131 may be delivered without damaging the surrounding tissues (2,3). However the molecular mechanisms, by which beta-irradiation causes cell death are not wholly understood. Necrosis, a passive death, and apoptosis, known as programmed cell death seem implicated in both processes. Few studies have attempted to identify the mechanisms by which beta-irradiation induces cell death in human tissues. By using morphological criteria apoptosis could be distinguished from necrosis. Necrosis leads to cell swelling, membrane lysis and release of organelles, while apoptosis is characterized by cell shrinkage, condensation of the cytoplasm and the chromatin, and nuclear fragmentation, forming small apoptotic bodies, as revealed in our case report (Figure 2). It may be noted that Guiraud-Vitaux, et al (8) had observed only necrosis in the thyroid of rats treated with therapeutic radioiodine dose. The destruction of the thyroid follicles was observed as early as 5 hrs after therapeutic administration but no animal was sacrificed after 48hrs (8). Yet, the characterisation of apoptotic cell death regarding the biochemical and molecular mechanisms as well as morphological changes seems to be important. Apoptosis may be initiated through different pathways: (1) the death receptor/ligand system that initiated apoptosis by engaging the tumour necrosis factor family, (2) the mitochondrial pathway that involved pro- and anti-apoptotic Bcl2 family members (9). Both pathways converge at caspase 3 activation, which triggers apoptosis. In vitro, beta-

irradiation can activate apoptosis pathway at several levels, including ligand/receptor pathways, mitochondrial activation and caspase activation, but its effect seems depend on the dose, time point and doses rate. At low dose rate a higher apoptosis was found than at high dose rate. Furthermore, low dose beta irradiation induced a cell cycle arrest in the G2/M phase and seemed acting such as a post-mitotic apoptosis, which occurs after cell division (10). Shinomiya, et al introduced two kinds of radiation-induced apoptosis, pre-mitotic and post-mitotic apoptosis. The former is induced by high dose irradiation that rapidly activates caspase 3 and triggers a rapid apoptosis, whereas the later shows a delayed apoptosis (11).

In humans, I-131therapy can induce apoptosis in hyper-functioning thyroid tissue by activating both the ligand/receptor and mitochondrial pathways (12). But, no systematic screening of apoptosis has been done on thyroid carcinoma treated by radioiodine. It may be noted that iodine concentration is heterogeneous. Its uptake varies from patient to patient and also dependent on the type of thyroid carcinoma; furthermore, in a given patient uptake varies among metastases. These variations are related to the heterogeneous expression of NIS (sodium/iodide symporter), an active transporter entering iodide ion into thyroid cells (13). Thyroid cancer tissues with NIS expression take up more I-131 than those without NIS expression, and show a higher rate of response to radioiodine treatment. NIS expression could be lost in metastatic tissues of differentiated thyroid carcinomas (14). Its expression is a prognostic factor. Multivariate analysis showed that four variables have a favourable impact on the distant thyroid-metastasis: a young age (under 40) at the time of metastases detection, the papillary or follicular well-differentiated histological type of the primary tumour, a small extent of disease, and the presence of I-131 uptake (2,15,16). I-131 uptake is more homogeneous when pulmonary metastases are under 1 cm, but a similar survival time could be observed in patients with fine miliary type versus those with macronodular metastases (mean time 27.4 ± 2.9 vs 17.5 ± 2.1 years) (7). Outcome depends on I-131uptake metastases. The overall survival rate at 10 years is 75% in I-131 avid pulmonary metastases versus 25% in I-131 non-avid metastases (7).

In the present case the I-131 uptake by pulmonary metastases should have lead to favourable outcome. Yet, the issue was a fatal sudden pulmonary haemorrhage occurring 21 days after therapeutic iodine. This event suggests that the high concentrating iodine was responsible for a massive synchronous cell death. As has been previously reported, apoptotic wave could be experimentally induced (17). The synchronous cell death, which appears after a delay of 21 days, that is the duration of the cell cycle, could be considered as a post-mitotic apoptotic wave induced by the beta particles. Acute alveolar injury can be the result of a massive apoptosis. Apoptosis is activated in the lung of patients with acute alveolar injury by activation of the soluble Fas ligand (sFasL), a soluble death/receptor ligand (18). Moreover sFasL instilled into alveoli induces alveolar haemorrhage (19). The fatal sudden alveolar haemorrhage was probably induced by an apoptosis wave, a consequent of the radioiodine.

This side effect of radioiodine is out of ordinary. Diagnostic iodine 131 imaging prior to I-131 ablative therapy may affect the outcome of high dose therapy, hence it is not done under normal circumstances (20). As long as pulmonary metastases are detected by whole body scan (WBS), radioiodine should be the therapy of choice. In many centres the dose of I-131 ablation is about 3.7 Gbq (100 mCi). A high I-131 activity detected in the lungs by WBS should involve particular care, and perhaps late discharge. A preparation with recombinant human thyroid-stimulating hormone could lower extra-thyroidal radiation, and has to be considered even when extra cervical metastases are detected.

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