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Occurrence of Thyroid Papillary Carcinoma in Young Patients. A Chernobyl Connection?

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ABSTRACT

The risk of thyroid papillary carcinoma is increased by external radiation particularly in children under 15 years of age as shown by a marked increase in those exposed to radiation after Chernobyl. We were recently confronted in Belgium over a short period with four patients (3 F, 1 M) with papillary thyroid carcinoma who were aged 10 years, 2 months, 2 years and 6 years when the Chernobyl accident occurred. We thus raise the question of a possible relationship. The patients were aged 17, 11, 10, 19 years at presentation. They all presented fortuitously over 3 years which was a very unusual increase in our extensive experience in thyroid surgery (62 cases of thyroid cancer among 1014 thyroidectomies in adults vs 4 cases in 18 children since the Chernobyl accident in 1986). Two out of the four patients had psammoma bodies (identifiable on CT scanning and ultrasound) and thyroglobulin autoantibodies (TgAb). The first patient had positive lymph nodes at the time of surgery. The incidence of thyroid cancers in Belarus and Ukraine rose just 4 years after the Chernobyl disaster; because radioactive clouds passed over Belgium, we wonder whether the occurrence of thyroid cancer in our patients could be related to this irradiation. The mechanism of increased incidence of radiation-induced thyroid cancer is thought to be due to rearrangement of the tyrosine kinase domains of the *RET* and *TTK* genes. The other important similarities in our patients are the presence of psammoma bodies that can be visualized on radiological examination and the presence of TgAb that are more frequent in differentiated thyroid cancers. Whether or not these cases reflect an increased incidence in the population as a whole, clinicians must remain vigilant for this rare but curable cancer in young patients, especially if suggestive radiological features or TgAb are present.

KEY WORDS

thyroid papillary carcinoma, irradiation, children

INTRODUCTION

Thyroid carcinomas are relatively rare comprising less than 1% of all human cancers and having a peak incidence at 45-50 years old[1]. Fewer than 10% of differentiated thyroid carcinomas occur in patients younger than 20 years old[2]. Thyroid cancer typically presents with an asymptomatic thyroid nodule. Virtually all patients are clinically and biochemically euthyroid. The risk of thyroid papillary carcinoma is increased by both external and internal radiation, particularly in children under 15 years of age, as shown by a great increase (up to 100-fold) in those exposed to radiation after Chernobyl[1,3,4]. We were recently confronted over a short period with four similar cases of papillary thyroid carcinoma in young patients, living in South-East Belgium, who were aged 10 years, 2 months, 2 years and 6 years, respectively, when the Chernobyl accident occurred. We thus raise the question of a possible relationship.

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PATIENT REPORTS

The first patient was a 17 year-old girl presenting with a painful swelling in her neck and difficulty in swallowing. On clinical examination, this was found to be a right-sided thyroid nodule that was cold on isotope scanning. The computed tomographic (CT) images without contrast injection, previously reported[5], disclosed concentrically layered punctate calcifications suggestive of psammoma bodies, which was confirmed by histopathology. Thyroid function tests were normal except for thyroglobulin autoantibodies (TgAb) which were raised up to 5000 U/ml (normal <50). Antithyroid peroxidase (anti-TPO) autoantibodies were absent. Tg was less than 0.05 ng/ml but the presence of TgAb make it impossible to interpret. The patient was treated by total thyroidectomy and lymph node dissection which revealed multiple microscopic foci of papillary carcinoma and two involved lymph nodes. She was then treated with four doses of ablative radioiodine therapy (100 mCi each). Three years after the initial operation, a small residual uptake of radioiodine was found in the cervical area and a 5 mm lymph node was suspected on ultrasound (US) examination. The patient underwent a new operation during which three retrosternal lymph nodes containing papillary carcinoma were removed. A fifth dose of radioiodine was then administered. The patient is now well and disease-free, being treated with 125 μg of thyroxine. Tg is undetectable and TgAb have disappeared.

The second patient was referred, aged 11, after a CT scan performed for a neck injury revealed punctate calcifications in the right thyroid lobe (Fig. 1a) that were similar to those found in the first patient. US examination confirmed the calcifications (Fig. 1b), and an isotope scan showed a heterogeneous goiter but no cold nodule. She was euthyroid but with raised TgAb of 456 U/ml. Tg was less than 0.1 ng/ml but, as in the first patient, not interpretable because of TgAb. Anti-TPO were undetected. She underwent a right lobo-isthmectomy which revealed multifocal diffuse sclerosing papillary variant with psammoma bodies and it was decided to re-intervene and remove the entire thyroid. She received radioiodine ablative therapy post-operatively (100 mCi). She was then substituted with thyroxine 125 μg/day. The patient is currently well and no more TgAb are detectable; Tg remains low.

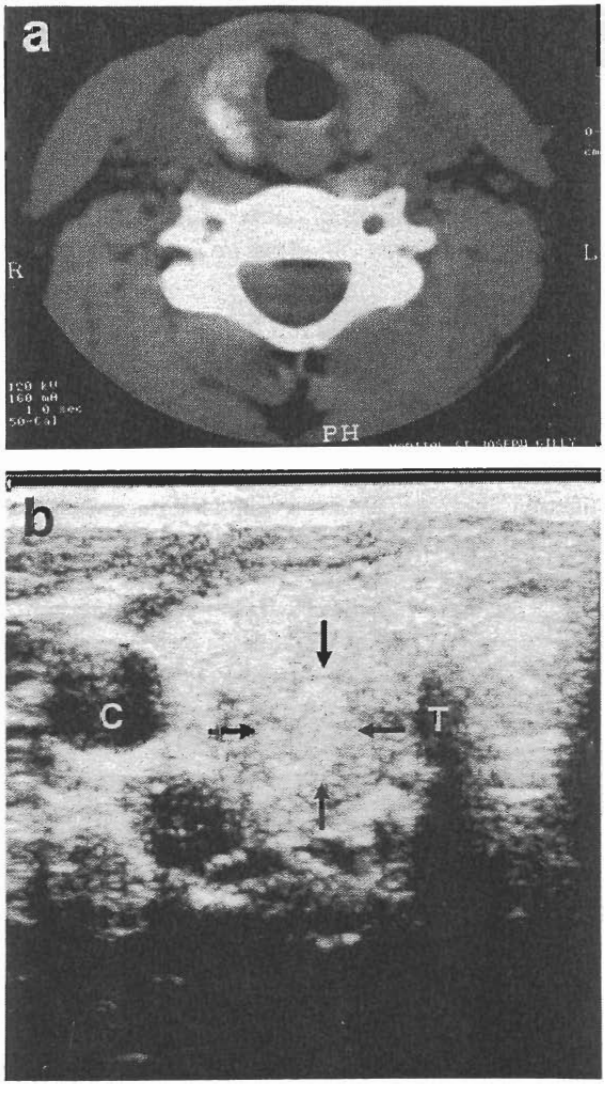

Fig. 1: Computed tomography (CT) (**a**) and ultrasound (US) (**b**) scans of the thyroid of patient 2, showing psammoma bodies. In the CT, punctate calcifications can be clearly seen on the right. In the US, microcalcifications (arrows) are observed inside the right lobe. C = carotid artery; T = trachea.

The third patient, a 10 year-old girl, was referred with a two-week history of painless neck swelling. Clinical examination revealed a nodule in the left thyroid lobe. US examination revealed a cystic hypoechogenic mass which was cold on thyroid scintigraphy. Thyroid function tests were normal

but Tg was increased at 370 ng/ml (normal <40); TgAb and anti-TPO were absent. She underwent a left hemi-thyroidectomy. Histology demonstrated a follicular variant papillary carcinoma.

The fourth patient, a 19 year-old man, presented with a painless right-sided nodule, that proved to be cold on isotope scanning and solid on US examination. A CT scan without contrast injection disclosed a 3.5 cm hypodense nodule without calcification. Thyroid function tests were normal. Neither TgAb nor anti-TPO were detected but Tg was slightly raised up to 62.7 ng/ml. A total thyroidectomy was performed because the nodule contained a follicular variant papillary carcinoma. One month later, the patient received a 100 mCi dose of ablative radioiodine and was then started on thyroid hormone replacement therapy.

DISCUSSION

The similarities in these four young patients with papillary thyroid cancer, who all presented fortuitously over a short period, surprised us as it was in contrast to our extensive experience in thyroid surgery. Indeed, since 26 April, 1986 (the date of the Chernobyl accident), 1014 thyroidectomies in adults were performed in our department, among which 62 cases of thyroid cancer were detected (6.1%). In contrast, during the same period, thyroid operations were performed in 18 children or adolescents, and these four cases of cancer were found over the last 3 years. Before April 1986, we did not operate on any childhood cancer, and the percentage of thyroid cancer found in adult patients undergoing thyroid surgery was 5%. Furthermore, since January 2000, we operated on five more female patients who were 8, 8, 10, 11 and 12 years old at the time of the Chernobyl accident, and 22, 22, 24, 25 and 26 years old at the time of diagnosis of papillary carcinoma follicular variant of the thyroid.

The incidence of thyroid cancers in Belarus and Ukraine rose just 4 years after the Chernobyl disaster, but the risk rises to a maximum 15-20 years after exposure and remains high for a further 20 years. Although announced in the media, the question of whether radioactive clouds passed over Belgium and other European countries is controversial. We therefore questioned the Belgian Royal Institute of Meteorology (BRIM)[6] in order to obtain data about the atmospheric radioactive exposure of the Belgian population at the time of the Chernobyl accident. In Belgium, the mean value of natural atmospheric radioactivity is 3.2 $Bq.m^{-3}$ per year[6]. From 1-3 May 1986 (arrival of the contaminated clouds from Chernobyl over Belgium), the mean daily value of radioactivity rose to over 70 $Bq.m^{-3}$ per day. By comparison, the mean daily value of radioactivity measured at ground level by the BRIM on 2nd and 3rd May, 1986 in Belgium was 20-fold higher than the mean daily values measured during and after a period of 110 important atmospheric nuclear bomb tests in 1961 and 1962; and a hundred times the radioactivity measured in Belgium (700 $mBq.m^{-3}$ per day) on 11th and 12th October, 1957, after the nuclear accident in Winscale, UK (now called Sellafield)[6]. Based on this high radioactive exposure, we thus wonder whether the occurrence of thyroid cancer in our patients could be related to the irradiation from Chernobyl. The mechanism of increased incidence of radiation-induced thyroid cancer is thought to be due to a rearrangement of the tyrosine kinase domains of the *RET* and *TTK* genes, which is found more frequently in papillary carcinomas associated with irradiation[7]. The *RET/PTC* rearrangement is restricted to papillary thyroid carcinomas and is thought to be an early event in tumorigenesis. The thyroid cancers in regions close to Chernobyl appeared to be more aggressive with a higher percentage of lymphatic and vascular invasion even in small tumors less than 1.5 cm in diameter.

Apart from age, the other similarities of our patients lie in the presence of psammoma bodies and TgAb in two out of four patients. Psammoma bodies classically appear as a microscopic finding consisting of calciferous globules (5-100 μm diameter), typically in association with papillary carcinoma where it is thought to be a slow growing process. Although calcification occurs in benign and cancerous conditions of the thyroid, this fine pattern of calcification can often be differentiated from more dense calcification and, as in our patients, can be detected by CT scans or US examination, an aspect rarely appearing in the literature. It is also noteworthy that one study found a good

correlation between punctate calcifications detected by US and histological psammoma bodies in metastatic lymph nodes[8]. The other similarity of our patients is the presence of TgAb whereas anti-TPO were absent. This is in agreement with the known increased prevalence of thyroid autoantibodies in patients with differentiated thyroid cancers compared with the general population[9,10]. In particular, a previous study has shown that serum TgAb (with or without anti-TPO) was present in 25% of patients with differentiated thyroid cancers and 10% of the general population[9]. It has been hypothesized that this increased prevalence of thyroid antibodies in thyroid cancers could be due to an enhanced presentation of thyroid tumor antigens to the immune system, although this point is controversial[9]. If Tg is a well-established tumor marker in the follow-up of these patients, it is also noteworthy that retention of TgAb positivity reflects persistent disease, whereas the loss of TgAb positivity suggests a cure[10]. Interestingly, TgAb disappeared in the two patients who were cured.

It is difficult to make a firm statement on the dose linkage between these thyroid cancers diagnosed in young people and post-Chernobyl radioactive exposure. However, it is also difficult to say that such links do not exist. Thus, we think it is important that clinicians remain vigilant for this cancer in young patients, especially if suggestive radiological features (punctate calcifications suggestive of psammoma bodies) or biochemical features (TgAb) are present. We also suggest that an epidemiological survey should be considered at a European level.

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