Papillary thyroid carcinoma after total body irradiation

Cornelio Uderzo, Maria Teresa van Lint, Attilio Rovelli, Giovanna Weber, Maria Rita Castellani, Andrea Bacigalupo, Nicoletta Masera, Amnon Cohen

Department of Paediatric Haematology and Oncology, S Gerardo Hospital, University of Milan, Monza
C Uderzo
A Rovelli
Bone Marrow Transplantation Unit, S Martino Hospital, Genoa
M T van Lint
A Bacigalupo
Department of Paediatric Endocrinology, S Raffaele Hospital, University of Milan
G Weber
N Masera
National Institute of Tumours, Milan
M R Castellani
University Department of Paediatrics, Paediatric Endocrinology Unit, Gaslini Institute, 16148-Genoa, Italy
A Cohen
Correspondence to:
Dr Cohen.
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Abstract
Two children developed papillary thyroid carcinoma after allogeneic bone marrow transplantation (BMT) probably due to radiotherapy during remission and pretransplantation conditioning. Establishing a relationship between the cellular thyroid stimulating hormone (TSH) effect and development of carcinoma in cases with high serum TSH concentrations is difficult. After BMT, patients should be regularly followed up with thyroid ultrasound and, when nodularity is found, fine needle aspiration and/or open biopsy are recommended. (Arch Dis Child 1994; 71: 256–258)

Papillary thyroid carcinoma can occur at any age and is seen more frequently in children and adolescents than other thyroid malignancies. High thyroid cancer incidence has been reported in survivors of atomic bombing. Young patients with papillary thyroid carcinoma generally have a history of radiotherapy for thymic enlargement, cervical lymphadenopathy, or Hodgkin’s lymphomas.1,2 Patients undergoing bone marrow transplantation (BMT) for haematological malignancies have proved to be at risk for second tumours.3,4 Although thyroid carcinomas have rarely been described,5 our experience shows this could be a malignant ‘late effect’ after BMT.

Case reports (see table)

CASE 1
A boy was diagnosed with acute lymphoblastic leukaemia (ALL) at 2 years of age (January 1978). Chemotherapy was initiated following the 7601 Italian cooperative study recommendations that included prophylactic cranial irradiation of 24 Gy two months after diagnosis. Complete continuous haematological remission was maintained until December 1982 when bone marrow and testicular relapse was noted.

Multiple drug chemotherapy treatment following the Italian protocol for recurrent leukaemia was started and a second complete remission achieved. In March 1984 allogeneic BMT from his HLA and mixed lymphocyte culture (MLC) compatible sister was performed. The conditioning regimen included cyclophosphamide in a dose of 60 mg/kg/day on two consecutive days and fractionated total body irradiation (TBI) in a dose of 3·3 Gy/day for three consecutive days delivered by a cobalt 60 source (dose rate 15 cGy/min).

He was treated for graft-versus-host disease (GVHD) with prophylactic cyclosporin and he was given a short methotrexate course. His post-transplant course was uneventful and no major complications or symptoms related to GVHD occurred. In March 1990, slightly high basal plasma thyroid stimulating hormone (TSH) concentrations were found (6·07 mU/l; normal values <4·5) with normal plasma concentrations of triiodothyronine and thyroxine. During the next two years, his TSH concentration remained at 3·7 to 5·31 mU/l, and triiodothyronine and thyroxine remained normal.

Thyroid ultrasonography (June and December 1991) showed a hypechogenic nodule (7 mm in diameter) in the middle third of the left thyroid lobe. A 99mTc thyroid scintiscan was normal.

Fine needle aspiration (April 1992), showed a second grade papillary thyroid carcinoma. Total thyroidectomy and cervical lymph node dissection two months later confirmed grade II multifocal papillary carcinoma. Further chemical thyroidectomy using 100 mCi of 131I

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Cy = cyclophosphamide.
was performed (January 1993) because of residual thyroid tissue in the anterior cervical region. A pulmonary computed tomogram was normal. In February 1994 the boy was well and treated with levothyroxine.

CASE 2
A boy, aged 12 years in August 1988, with ALL-L3 according to French-American-British classification had complete remission achieved using the AIEOP-8805 protocol. Allogeneic BMT from his HLA and MLC compatible sister was performed in December 1988. The conditioning regimen consisted of cyclophosphamide (60 mg/kg/day on two consecutive days) and fTBI (2 Gy twice daily for three consecutive days), delivered by a linear accelerator, with a dose rate 7.5 Gy/min.

After transplantation he was treated with cyclosporin for GVHD prophylaxis. His post-transplant course was uneventful, although he developed ‘de novo’ chronic GVHD 19 months after BMT. GVHD disappeared after 2 years’ treatment with cyclosporin.

In September 1990 an abnormally high basal plasma TSH concentration was observed (6.2 mU/l) with normal plasma concentrations of triiodothyronine and thyroxine. Thyroid ultrasound examination (July and December 1991) revealed a hypoechogenic nodule (9x10.4 mm in diameter) on the upper pole of the right lobe. A 99mTc thyroid scintiscan was normal.

Fine needle aspiration was carried out twice (March and September 1992) and failed to provide adequate information, probably because of altered, thickened skin due to chronic GVHD. Serum thyroglobulin was raised (240 ng/ml). Thyroidectomy performed two months later was consistent with multifocal, second grade papillary thyroid carcinoma with metastatic spread to adjacent cervical lymph nodes, bilaterally.

Two courses of ablating doses of 131I (150 mCi each) were given after residual thyroid tissue had been seen during a postoperative 131I whole body scan. The patient is well at the time of this report.

Discussion
An increased incidence of second tumours has been reported in children successfully treated for primary malignancies and in patients after BMT for haematological malignancies. The two patients reported had no family history of thyroid goitre or dysfunction, and were not from areas of endemic goitre due to iodine deficiency. Neither patient typed HLA-DR1 and/or B35. Ten per cent of normal thyroid glands studied at necropsy are found to have microscopic papillary thyroid carcinomas. It is therefore accepted that latent malignant cells exist in thyroid tissue years before carcinoma diagnosis and that irradiation, especially during childhood, is the trigger for development of carcinoma. We cannot exclude, therefore, occult papillary thyroid cell carcinoma in our two patients years before transplant. ALL patients who have received irradiation treatment have an increased risk of second neoplasms particularly in the central nervous system. In 9720 patients, 43 second tumours were reported. All 23 patients with central nervous system tumours had cranial irradiation. Furthermore, 32 of the 43 second neoplasms appeared in previously irradiated fields. No data have been reported concerning the three patients who developed thyroid cancer. The first of the two patients we report received irradiation twice (24 Gy cranial irradiation during first line treatment and 10 Gy of fTBI before BMT as part of conditioning regimen). The second received only fTBI three years before diagnosis of thyroid carcinoma. Irradiation fields involved the thyroid region in both patients. The period between irradiation and diagnosis is different in the two patients but is much shorter than the 25–30 year latency period usually observed in patients developing thyroid cancer after irradiation exposure for reasons other than cancer. In following up long term survivors after BMT, care must be taken to exclude the presence of a thyroid tumour, especially when fTBI was used during pretransplant conditioning.

Up to 40% of patients exposed to cervical irradiation in doses of 40–50 Gy, as treatment for Hodgkin’s disease or cranial tumours, had some degree of thyroid dysfunction. Compensated, subclinical hypothyroidism (high TSH with normal thyroxine concentrations) has also been reported after BMT with varying incidence. The hypothesis that high serum TSH concentrations constitute the trigger for the induction of thyroid tumour cells through a growth effect on thyrocytes cannot be excluded.

Thyroid dysfunction, with raised TSH due to primary hypothyroidism, was observed six and two years respectively after TBI in our cases. Ultrasound examination revealed multinodular goitre (not clinically palpable) but thyroid scanning did not help in diagnosis. Fine needle aspiration confirmed malignancy in one patient. The other had high serum thyroglobulin concentrations.

Thyroid carcinoma is curable if diagnosed early and treated promptly. We suggest serum thyroglobulin be measured regularly in patients after BMT, to help predict thyroid carcinoma. Ultrasound and fine needle aspiration are keystones in management of transplanted patients with thyroid nodules. Suspicious cases, with doubtful results on fine needle aspiration (as found in case 2), should undergo open thyroid biopsy.

After BMT patients should be examined carefully for second tumours, and especially for thyroid cancers, especially if they had been irradiated. Patients with compensated hypothyroidism, or thyroid nodularity appearing after BMT, should be considered for thyroid hormone treatment to reduce pituitary TSH secretion which might thereby lessen the risk of developing papillary thyroid carcinoma. It is less clear whether to recommend inducing TSH suppression with levothyroxine treatment in all patients after neck irradiation, even if
thyroid dysfunction and nodularity are absent. The risk of inducing osteoporosis, especially in females, should not be disregarded.

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