Multiple Bone Metastases in a Patient with Differentiated Thyroid Cancer (DTC)

Complete resolution following thyroidectomy and four ablation doses of I-131

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Abstract: Multiple bone metastases from a differentiated thyroid cancer are usually incurable. We report the case of a young Omani woman who presented with 8 discrete skeletal lesions three years after a total thyroidectomy. Following four ablation doses of I-131 she has remained in clinical and biochemical remission for over five years. An extraordinary aspect of this case was the persistent refusal of her husband to use contraception either for himself or his wife. This resulted in her treatment being delayed for more than 6 years during which time the patient delivered and breastfed four additional healthy babies.

Keywords: Differentiated thyroid cancer; Thyroidectomy; Resolution of bone metastases; I-131 ablation.

In differentiated thyroid cancer (DTC), metastases occur outside the neck in up to 15% of patients and less than 3% of these are in bone.12 Their early detection is made possible by measurement of serum thyroglobulin (Tg) and by whole body scanning (WBS) using I-131. Thyroglobulin is synthesised by all thyroid tissue except anaplastic cancers and, when detected after all non-malignant tissue has been destroyed, indicates the presence of residual DTC. Thyroid stimulating hormone receptors (TSH-R) are present on most but not all DTC metastases. If present, Tg levels usually increase when the patient is hypothyroid, off thyroxine (T4) with elevated endogenous thyroid stimulating hormone (TSH) levels, or after injections of recombinant human TSH (rhTSH) with the patient euthyroid on T4 replacement.13 For those patients without a Tg response to TSH and those who do not take up I-1314, other treatments must be employed as indicated, for example, additional surgery, external radiotherapy, embolisation, etc.5

Treatment guidelines for DTC include total thyroidectomy and removal of any nodal metastases followed by an ablation dose of I-131 4–6 weeks later when TSH levels are elevated.6 This first dose destroys residual normal tissue and may localise any metastatic disease.7 After a further 6 months an I-131 WBS is carried out after withholding T4 or using rhTSH. If the WBS is positive, a further ablation dose is given and the process repeated, when indicated, at 6 monthly intervals until there is no further I-131 uptake. Thyroglobulin measurements are more sensitive than WBS for detecting metastases; however, up to 6% of patients
may have functioning metastases when serum Tg and Tg antibody levels are unmeasurable.\(^8\)

In this paper, we present details of a young patient who developed multiple bone metastases and whose treatment, both surgical and isotopic, was delayed by multiple pregnancies, the husband refusing contraception for his wife or for himself. In spite of this, and following surgery and four ablation doses of I-131, the patient has remained in clinical and biochemical remission for more than five years.

**Case Report**

The patient aged 20, a mother of four children, presented, in 1996, to another hospital in Oman with a large multinodular goitre. Surgery was advised, but delayed until 1999 because of two further pregnancies. After a total thyroidectomy, the histology confirmed a follicular variant of papillary thyroid carcinoma with capsular and vascular invasion [Figures 1 & 2] without lymph node involvement. She was then referred to Sultan Qaboos University Hospital, Oman, for I-131 ablation. Her clinical examination at that time and thyroid function tests were normal with an undetectable Tg level on T4 replacement. She was admitted one month later, having stopped T4, at which time the Tg level was 39 ng/ml. Unfortunately, treatment had to be postponed as she was again pregnant (for the seventh time). Abortion was offered, but refused, and, as a result of the families’ insistence on breast feeding, her first ablation dose was delayed for an additional 2 years until July 2001. The Tg had now risen to 513 ng/ml off T4, and the post I-131 ablation whole body scan (WBS) revealed uptake in the thyroid bed and extensive metastases involving the skull, dorsal and lumbar spine, pelvis, right hip, right humerus, sternum and ribs [Figure 3]. These were not visible on a routine skeletal survey. Additional I-131 ablation doses were planned every 4–6 months and the family was again advised to use contraception until the patient’s treatment was complete. This advice was ignored. The second ablation dose was given 6 months later in January 2002. With the patient off T4, the Tg had now decreased to 164 ng/ml, but the WBS still revealed extensive asymptomatic metastases, but without any uptake in the neck. A further pregnancy (number 8) delayed the third ablation for another two years until November 2004. At this time, however, the Tg was only 2 ng/ml off T4 and the WBS had become negative. She received a fourth ablation dose in March 2006 although the Tg was undetectable off T4.
and the WBS remained negative. Pregnancy number 9 was uneventful and her Tg levels have remained undetectable on T4 for more than 6 years [Figure 4]. Thyroglobulin antibodies were undetectable throughout. Lactation was discontinued 3 months before the first and third ablation doses of I-131. The patient was not lactating before the second and fourth doses. Each time, ablation doses were given after stopping T4 for one month. The TSH levels were >100 on each occasion.

**Discussion**

Patients with DTC have a 10-year survival rate of 80–95%. This drops to 40% when distant metastases are present and to less than 21% when these are in bone. Bone metastases are from mainly follicular or less well differentiated tumours and 80% occur within the axial skeleton, which contains a large number of stored growth factors. Tumour cell products inhibit osteoprotegerin production thus permitting increased interaction of the receptor activator of nuclear factor kappa beta (RANK) and its circulating ligand (RANK-L). This results in excessive bone resorption with release of transforming growth factor beta (TGF-β), platelet derived growth factor (PDGF) and insulin like growth factor (IGF), amongst others, which stimulate further tumour growth. Remission rates for single lesions may be as high as 54%, but this falls to less than 3% with multiple bone metastases and usually occurs in those patients...
under 45 years of age with a small tumour burden and normal appearing skeletal X-rays. This was the case in our patient whose metastases developed 18 months after the delayed thyroid surgery. The I-131 ablation doses were widely spaced due to her intervening pregnancies. Rising outpatient Tg levels and I-131 WBSs confirmed the presence of multiple metastases which were confined to the skeleton, but not visible on routine skeletal surveys.

Our patient’s situation was most unusual as contraception was refused throughout. However, the prevailing view is that pregnancy has no major influence on the prognosis of DTC. Nonetheless, the resultant delays and the effects of her pregnancies undoubtedly encouraged the development of the metastatic disease. In spite of this, her Tg level was undetectable at the time of her fourth admission. Nevertheless, we elected to give another ablation dose in an attempt to destroy any microscopic foci of residual disease or functioning metastases that may be present when Tg and Tg antibody levels are negative. At this point, the WBS was negative and the Tg levels have remained undetectable since then.

**Conclusion**

Inspite of all the delays in this patient’s treatment, it appears that her DTC with multiple bone metastases has been cured.

**References**

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