Vitamin D3 Treatment for Locally Advanced Thyroid Cancer: A Case Report

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Abstract. There are many intricacies in the surgical treatment of locally advanced thyroid cancer, including the medical management of the remaining functional organ and any cosmetic impairments, which are sometimes very difficult to manage and eventually carry a relatively high morbidity and mortality. Here, we report on a case of a 65-year-old female with an extremely locally-advanced thyroid cancer involving both lobes of the thyroid, blood vessels, trachea and esophagus. Despite the severity of her condition, oral administration of vitamin D3 (alphacalcido) has stalled both the tumor growth and further increases of serum thyroglobulin (Tg) level, and has led to a good preservation of quality of life for the last two years. Several reports have previously demonstrated the efficacy of vitamin D3 to inhibit the proliferation of thyroid cancer cell lines *in vitro*, but clinical evidence has been limited so far. Therefore, this case report provides important evidence for the effectiveness of vitamin D3 therapy against advanced thyroid cancers.

Key words: Advanced thyroid cancer, Vitamin D3, Thyroglobulin, Dormancy

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THE most radical treatment for thyroid cancer is surgical removal of the tumor. However, it is sometimes very difficult to assess whether such an operation is appropriate when the tumor is advanced and has invaded neighboring tissues such as esophagus, trachea, nerves and blood vessels, etc. Moreover, the surgery may sometimes lead to an unacceptable outcome with severe impairment of the patient's quality of life.

Several reports have already demonstrated that 1,25-dihydroxyvitaminD (calcitriol), an active metabolite of vitamin D3, exerts an antineoplastic effect on several cancers such as those of colon, prostate and breast [1–4]. In addition, vitamin D3 has been shown to inhibit

the proliferation of various thyroid cancer cell lines *in vitro* [5, 6]. Recently, Dackiw *et al.* reported that calcitriol administration reduced the tumor burden and inhibited metastatic growth in an animal model of thyroid cancer [7]. However, there are few clinical studies that have evaluated the effectiveness of vitamin D3.

In this report, we present a patient diagnosed with locally advanced thyroid cancer whose tumor growth has been stabilized for 2 years following treatment with a low dose of oral vitamin D3.

Case Report

A 65-year-old Japanese female first noticed a lump in her neck and difficulty swallowing in October 2002. She also suffered from hoarseness, aspiration of food and a weight loss of 14 kg (from 56 to 42 kg) over 6 months. As the lump continued to enlarge, she was referred to our hospital for further evaluation and treat-

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ment in March 2003. We found nothing to suggest thyroid nodules in her past medical history. The lump in her neck was more than 10 cm in diameter and had poor mobility. Ultrasonography (US) and computed tomography (CT) scans of the neck showed a large thyroid tumor consisting of both small and large cysts and solid components with calcification. Furthermore, the tumor had invaded the other side of the thyroid, passing through the dorsal part of the trachea and involving the recurrent nerve, carotid artery and esophagus. Blood test results showed a normal level of thyroid hormone but significant elevation of thyroglobulin (Tg) (213.6 $\mu\text{g/l}$). Fine needle aspiration cytology of the tumor revealed thyroid papillary carcinoma (Fig. 1).

The patient consistently refused to undergo surgery to remove the tumor and involved tissues, although she was informed that the prognosis of her thyroid cancer would be poor without surgical treatment. To reduce the volume of the tumor, some fluid was aspirated from the cystic lesions of the tumor, after which she was able to breathe more easily and eat semi-solid food. Therefore, this aspiration procedure from the tumor was continued on an almost weekly basis, draining a volume of around 90–100 ml each time. In addition, to further stabilize the cancer, the oral administration daily of 0.5 $\mu\text{g/body}$ of Alphacalcido (Alpharol®), a precursor of 1 alpha, 25-dihydroxyvitamin D3, was started in June 2003. Informed consent was obtained from this patient and she was informed that Alphacalcido (Alpharol®) was commonly used to treat osteoporosis, but had not yet been approved officially as a treatment

for thyroid cancer. Serum calcium level was within the normal range both before and after the Alphacalcido administration. Serum Tg level was 824.2 $\mu\text{g/l}$ in May 2003 but decreased to 265 $\mu\text{g/l}$ in July 2003. Tg level dropped further to 219 $\mu\text{g/l}$ in February 2005. The general condition of the patient has been stable up to the present date, April 2005. CT scan showed no significant changes in the diameter of the tumor size, and no evidence of distant metastasis was found during this period (Fig. 2). Furthermore, weight loss, anemia and hypoproteinemia have been stabilized over these 2 years.

Fig. 1. Aspiration cytology presented abnormal cell clusters with large cells showing irregular nuclear size, high nucleocytoplasmic ratio, irregular nuclear membrane, increased chromatin and obvious nuclear cytoplasmic pseudoinclusion. (Giemsa stain, $\times 400$)

Fig. 2. CT of transversal section. Scans were carried out in April 2003 (A) and February 2005 (B).

Discussion

Thyroid carcinomas exhibit a wide range of differentiation from indolent carcinomas such as micro-papillary carcinoma diagnosed at autopsy, to the most aggressive human malignancies, anaplastic carcinoma. Differentiated thyroid cancers usually present a good prognosis after surgical removal of the tumor, but when the tumor has invaded blood vessels, nerves, esophagus and trachea, a complete excision may compromise their functionality as well as the safety of operation. In such cases, an alternative treatment would be desirable.

Recently, new therapies for recalcitrant thyroid cancer have been proposed. Gene therapies based on different strategies such as p53 reintroduction, suicide gene therapy or re-expression of the sodium iodide symporter (NIS) have shown some effectiveness in animal models, but the safety and efficacy of such therapies in man are still controversial [8–10]. Redifferentiation therapy using retinoic acid (RA) has also been attempted *in vitro* and in animal models, but its clinical effectiveness has yet to be demonstrated [11, 12]. Immunotherapy using specific antigens such as CEA for medullary thyroid cancer has also been investigated in a phase I clinical trial, but its efficacy proved too limited for practical use [13]. Therefore, practical and effective therapies are still necessary for those thyroid cancers where surgical treatment is not possible.

The role of vitamin D3 in the modulation of proliferation and differentiation, the reduction in invasiveness and angiogenesis, and the induction of apoptosis has been identified in a variety of cancerous cell types, including those of breast, prostate and colorectal cancers [1–4]. In one study, large doses of calcitriol were required to obtain antineoplastic effects, however, in another study, a reduction in the level of prostate specific antigen was reported using a daily oral dose of 0.5 to 1.5 μg of calcitriol in patients with prostate cancer [14, 15]. Currently clinical trials are in progress to examine the effectiveness of 1,25-dihydroxyvitamin D3 (calcitriol) for prostate cancer, and the synergistic and/or additive effects of vitamin D3 with cytotoxic chemotherapies are also under investigation [16, 17].

In terms of thyroid cancer, there have been several reports on the efficacy of vitamin D3 to inhibit proliferation and to induce re-differentiation of thyroid cancer cell lines *in vitro* [5, 6]. Recently, similar results have also been reported in animal models and thus clinical trials are anticipated for further investigation on the therapeutic role of vitamin D3 in thyroid cancer [7]. In our case, the dose of Alphacalcido (Alpharol®) administered was low enough (0.5 $\mu\text{g}/\text{body}/\text{day}$) to keep the serum levels of calcium and 1 alpha, 25-dihydroxyvitamin D3 within the normal range during the treatment. Thus, side effects of 1 alpha, 25-dihydroxyvitamin D3 such as hypercalcemia were avoided. On the other hand, the size of the solid components of the tumor barely changed during the period of vitamin D3 therapy, although no information on this aspect was available before the therapy was started.

In future, it is important to collect data of similar cases in order to establish the indications of vitamin D3 for induction of dormancy or stabilization of tumor growth in patients with thyroid cancer. A pooled analysis of multicenter joint studies under a common standard protocol should be formulated. The biopsy sample in our case was negative for BRAF mutation (data not shown), suggesting a relatively good prognosis. The relevance and significance of BRAF mutation in vitamin D3 treatment for thyroid cancer remains to be clarified [18, 19].

In summary, we report here a unique case of a locally advanced papillary carcinoma of the thyroid involving multiple tissues in the neck, where the tumor size was successfully stabilized following vitamin D3 treatment for 2 years. This case report provides a useful example of an alternative treatment for locally advanced thyroid cancer that was not amenable to surgical removal. However, more data must be collected before the efficacy of this treatment can be properly evaluated.

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