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Case Report

Successful Reinduction Therapy by Sorafenib in Oncocytic Follicular Thyroid Cancer: a Case Report

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Abstract

Introduction: Patients with iodine-refractory, locally advanced or metastatic differentiated thyroid cancer usually have a poor prognosis. As new therapeutic options, tyrosine kinase inhibitors may slow down progression and stabilize the disease. The resumption of therapy after progression of the disease is questionable.

Presentation of case: We report a case of a 68 year-old woman diagnosed with oncocytic follicular thyroid cancer with disease duration of 15 years. She was treated by bilateral subtotal thyroid resection, total thyroidectomy, three high-dose radioiodine treatments and two irradiation therapies. Sorafenib therapy was started in February, 2012, due to disease progression with lymph node and pulmonary metastases. The disease was stabilized for 20 months and then progression in the metastatic cervical lymph nodes was detected with rapid elevation of thyroglobulin level. After the surgical removal of lymph nodes, the sorafenib therapy was reintroduced in July, 2014 and the treatment has been effective until today.

Discussion: In this patient with a radioiodine-refractory, poor-risk oncocytic follicular thyroid cancer, the sorafenib therapy resulted in stable disease for 20 months and after progression and repeated surgical intervention the reinduction therapy was effective.

Conclusion: Sorafenib may be a useful therapeutic possibility in the management of oncocytic follicular thyroid cancer with distant metastases. If the tumor mass can be reduced by surgical intervention, reinduction therapy with sorafenib should be considered.

ABBREVIATIONS

CT: Computed Tomography; DTC: Differentiated Thyroid Cancer; FNAB: Fine-Needle Aspiration Biopsy; PET/CT: Positron Emission Tomography/Computed Tomography; RAI: Radioiodine; rTSH: Recombinant Thyroid-Stimulating Hormone; SPECT/CT: Single-Photon Emission Computed Tomography/ Computed Tomography; Tg: Thyroglobulin; TKI: Tyrosine Kinase Inhibitors; US: Ultrasound

INTRODUCTION

Iodine-refractory, locally advanced or metastatic differentiated thyroid cancer [DTC] usually have a poor prognosis in comparison to other thyroid cancer types as conventionally used therapeutic strategies may be less effective in these cases. Oncocytic follicular thyroid tumors have reduced capacity to uptake radioactive iodine and therefore less responsive to radioactive iodine therapy. In recent years, tyrosine kinase inhibitors [TKI] have been brought new opportunities for the management of thyroid cancers. Sorafenib [Nexavar®] was the first TKI approved for the treatment of iodine-refractory, locally advanced or metastatic DTC [1]. Through the inhibition of tyrosine kinases and RAF serine/threonine kinases, sorafenib has a great impact on tumor cell proliferation and angiogenesis [2]. Based on previous data, sorafenib proved to be a potent systematic therapy. Orally administered sorafenib in 400 mg twice daily dose may slow the progression of disease in the majority of cases and it may significantly prolong median progression-free survival [1,3-6]. Unfortunately, sorafenib shows a remarkable toxicity and can cause severe side effects, the most common are hand-foot skin reaction, diarrhea, and alopecia, and therefore dose reduction or discontinuation of treatment may be required in some cases.

In this case we presented a patient with metastatic oncocytic follicular thyroid carcinoma, who received sorafenib therapy for 20 months and then progression of cervical lymph node metastases was detected. After the surgical removal of metastatic lymph nodes, the sorafenib therapy was continued and the lung metastases of the patient were stable for another 23 months.

CASE PRESENTATION

We report a 68-year-old woman. Past medical history was not a factor and there was no family history of thyroid cancer either, although close relatives had various malignant diseases. In 2001, fine-needle aspiration biopsy [FNAB] of the thyroid raised the suspicion of cytological malignancy. The patient was referred to a thyroid surgeon and bilateral subtotal thyroid resection was carried out. Histological examination confirmed the diagnosis of oncocytic follicular carcinoma of the thyroid; the tumor was in dimension of 3.5 cm without any lymph node involvement [pT2a, Nx, Mx]. In 2006 October, a total thyroidectomy and neck exploration were performed due to local recurrence and lymph node metastases. Pathologic findings in thyroid gland are showed in Figure (1). Furthermore the patient received an irradiation therapy to the neck with 49.8 Gycumulative dose. Computed tomography [CT] scans of the chest were done but no positive findings were noted. After one year patient was presented complaining a small growing mass on the right side of her neck. During ultrasound [US] examination a hypoechoic nodule [measuring 10x5 mm] was detected arising from the right residual thyroid tissue; while elevated thyroglobulin [Tg] 42,1 ng/mL [normal range: 1,4-78,0 ng/mL] and anti-thyroglobulin antibody [aTg] 124,1 IU/ml [normal range: < 40 IU/ml] levels were presented. Due to these findings, patient received high-dose [3700 MBq] radioiodine [RAI] therapy with recombinant thyroid-stimulating hormone [rTSH]. Post therapeutic ^{131}I single-photon emission computed tomography/computed tomography [SPECT/CT] was done with no positive findings. Three months later, in the background of further rise of the tumor markers, abnormal isotope accumulation on the right side of the thyroid cartilage was identified on positron emission tomography/computed tomography [PET/CT]. At the end of 2008 patient received the second high-dose [3700 MBq] RAI treatment, SPECT/CT results were negative. In 2009 October Tg level was 616.8 ng/mL, and pulmonary metastases were observed during the second PET/CT examination (Figure 2). Furthermore a 6 mm lesion was found in the ninth segment of the left pulmonary lobe, which could not be clearly characterized, while the size of the previously identified mass with abnormal accumulation on the right side of the thyroid cartilage was not changed. According to decision of the oncoteam, patient received the second irradiation therapy with 50 Gy cumulative doses to the known pulmonary metastasis. Slow but continuous progression with recent bilateral pulmonary metastases led to the third high-dose [3700 MBq] RAI treatment. SPECT examination did not show abnormal isotope accumulation, but the previously identified bilateral pulmonary metastases could be identified on the CT pictures. In 2012, with extremely elevated Tg level, >1000,0 ng/mL, some nodes with approximately one cm size were palpable on the left side of the larynx and in front of the sternocleidomastoideus muscle. US and FNAB examinations confirmed the malignancy (Figure 3). A lymph node metastasis with 8 mm was found on the left side of the neck, while a lymph node conglomerate with 16 mm was identified on the right side of the thyroid cartilage. In 2012 February, due to lymph node and radioiodine-refractory pulmonary metastasis, sorafenib treatment was started with 2x400 mg daily dose. Initially a remarkable reduce in Tg levels was observed and neck/chest CT showed a stable disease

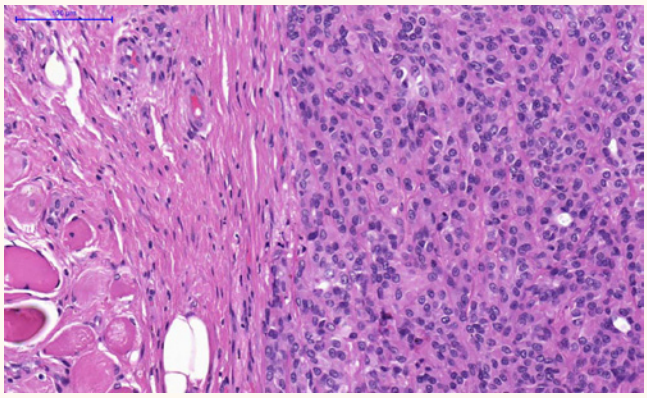

Figure 1 Hematoxylin and eosin (HE) staining of oncocytic follicular thyroid cancer; the image was magnified 20 times. Oncocytic cells showing abundant eosinophilic granular cytoplasm and prominent nucleoli.

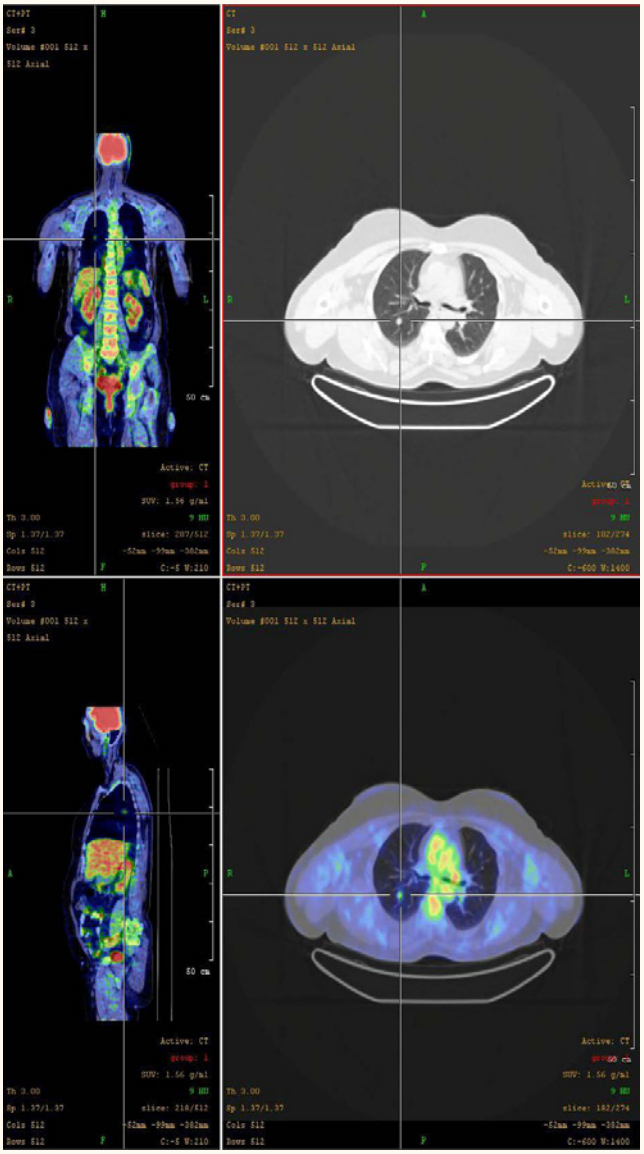

Figure 2 PET/CT showed a pulmonary metastasis with 9 mm diameter in the sixth segment of the right pulmonary lobe.

[radiologic response to sorafenib was classified according to the Response Evaluation Criteria In Solid Tumors System criteria, RECIST]. Various side effects of sorafenib treatment appeared, such as moderate hand-foot syndrome, diarrhea, weight loss [8 kg within 3 months] and alopecia. Symptoms could be relieved successfully with dose reduction [to 2x200 mg daily] for ten days and supportive medical treatment. During the next twenty months, Tg levels showed a significant increase, from 190.9 ng/mL to 2170, 0 ng/mL, while imaging techniques did not show any change in the state of disease. Then in 2013 October, physical examination revealed palpable nodules with approximately 1-1.5 cm diameter on both side of the neck. FNAB results confirmed the lymph node metastases of the primary disease. Sorafenib treatment was stopped due to the progression. At the beginning of 2014, surgical removal of the pathologic lymph node metastases was performed [Tg level decreased from 3570 ng/mL to 882 ng/mL] and then sorafenib therapy was restarted in 2014 July in 2x400 mg dose. No other treatment was used after sorafenib reintroduction. In 2016 June, at the end of follow-up the patient was in stable condition with sorafenib [Tg 713.9 ng/mL]. Changes of thyroglobulin levels during the course of the disease are presented on Figure (4).

DISCUSSION

It was known from earlier clinical data that sorafenib is an effective therapeutic option for iodine-refractory, locally advanced or metastatic DTC. Appropriate starting dose is questionable, many clinicians try to use a smaller than 800 mg starting dose to eliminate or reduce the appearance of adverse effects, and it seems that reduced daily dose is not influence negatively the efficacy of sorafenib, although according some findings reduced starting doses not necessarily lead to better tolerability [7]. Nowadays other promising results were published with lenvatinib, sunitinib and selumetinib [8-10].

We presented a patient suffering from oncocytic follicular thyroid carcinoma with 15 years of disease duration. Radioiodine-resistance and PET positivity indicated the poor prognosis of the tumor. The patient had two thyroid operations and received three high-dose radioiodine treatments and two irradiation therapies. Despite of the conventional treatment options, disease showed progression from time to time. She was one of the first patients in Hungary receiving sorafenib therapy. Therapeutic response to sorafenib treatment was really good, although several side effects developed like hand-foot syndrome, diarrhea, weight loss and alopecia. After 20 months of treatment, progression was detected in the cervical lymph node metastases but not in the pulmonary metastases. After the surgical removal of metastatic lymph nodes, the sorafenib therapy was continued and has been effective to stabilize the disease until today. Thyroglobulin level was more sensitive predictor of disease recurrence than imaging techniques.

In conclusion, sorafenib is an effective option for iodine-refractory, locally advanced or metastatic DTC. Adverse effects are mostly manageable and well-tolerated. Clinicians should carefully evaluate the use of systematic sorafenib treatment with the consideration of individual basis.

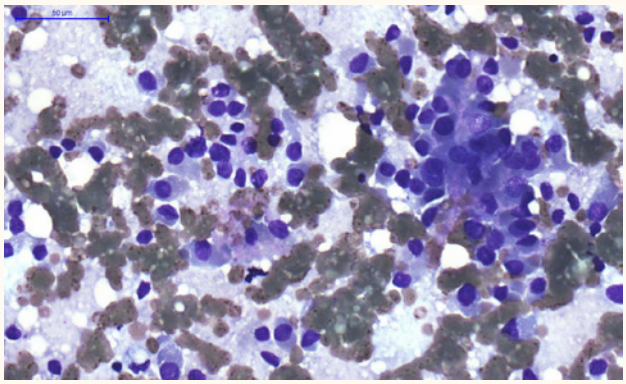

Figure 3 Giemsa staining of cytological specimen from fine-needle aspiration of metastatic cervical lymph node; the image was magnified 40 times.

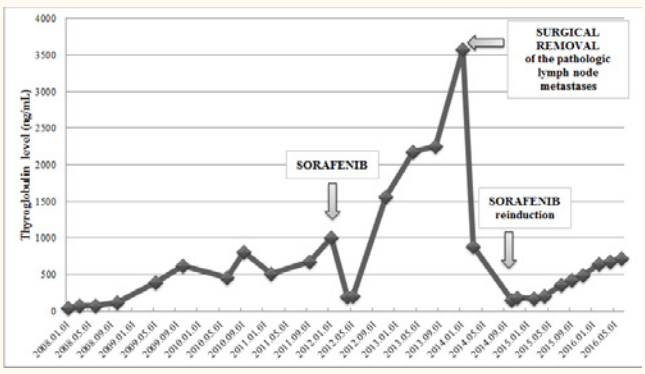

Figure 4 Changes of thyroglobulin levels during the course of the disease.

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