Pertechnetate Thyroid Scan and Thyroid Function Tests in a Case of Sorafenib Induced Thyroiditis

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Citation

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Abstract

Purpose of report:Sorafenib is a tyrosine kinase inhibitor used for treatment of advanced metastatic renal cell carcinoma and in recent years, for patients suffering from hepatocellular carcinoma (HCC) with limited options. Thyroiditis is a relatively rare side effect and we present one such case.Materials and Methods:We describe a 65 year old male undergoing Sorafenib treatment for advanced HCC, who developed thyroid abnormalities clinically and biochemically. Thyroid Function Tests followed over 6 months and a Tc-99m Pertechnetate scan were performed for diagnosis and evaluation.Results:The temporal connection between onset of clinical and biochemical hyperthyroidism with commencement of Sorafenib therapy in a patient with no history of thyroid disease aroused suspicions for a drug induced reaction. Follow-up over 6 months using TFTs and the thyroid scan confirms a thyroiditis with subclinical hypothyroidism that was preceded by a hyperthyroid phase.Conclusion:Correlation between TFTs and thyroid scans are useful in patients on Sorafenib therapy especially if there are clinical signs or if patients have risk factors of advanced age, prior thyroid disease or neck irradiation.

INTRODUCTION

Drug induced thyroiditis is often painless with patients mainly presenting with incidental abnormal thyroid function tests or less commonly clinical hyperthyroidism or hypothyroidism. The drugs most often associated with thyroiditis are interferon-alfa, interleukin-2, amiodarone, or lithium. Here we present a case of Sorafenib induced thyroiditis in a 65 year old man with advanced Hepatocellular Carcinoma (HCC). Sorafenib is a multikinase inhibitor that has already been approved for the treatment of metastatic Renal Cell Cancer (mRCC). Sorafenib targets the Raf/mitogen-activated protein kinase/extracellular signal–related kinase (ERK) signaling pathway as well as other tyrosine kinases like vascular endothelial growth factor receptor and platelet-derived growth factor receptors which are important for tumor cell proliferation and angiogenesis. The phase III Sorafenib HCC Assessment Randomized Protocol (SHARP) trial[1] demonstrated a significant survival benefit (placebo, 7.9 months; sorafenib, 10.7 months) and good tolerance in patients with HCC, making sorafenib the new reference standard for systemic therapy of patients with advanced HCC in 2006. To date there have been 3 studies looking into thyroid abnormalities post Sorafenib treatment in mRCC. Here we describe the work-up and diagnosis of Sorafenib induced thyroiditis in this patient.

CASE REPORT

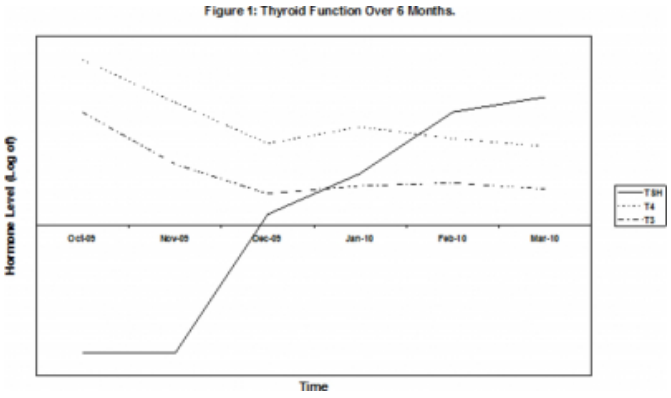
A 65 year old man was diagnosed with HCC and had a right hemihepatectomy in 2006. Following that, there were a further 4 occasions where he required Transcatheter Arterial Chemo-Embolisation (TACE) for recurrence of the HCC over the period from July 2007 to December 2008. In March 2009, during a routine follow-up scan, new peritoneal deposits, a left lung lesion and persisting liver lesions were found. Due to the advanced nature of the disease and limited treatment options, Sorafenib was commenced within 2 months, from 200mg daily (1 week) to 400mg daily (1 week) and finally the full dose of 400mg BD (in the 3rd week).

4 months post initiation of the systemic treatment, he developed symptoms of weight loss, loss of apetite and tremors. There was however no pain or tenderness associated with his thyroid gland. Thyroid Function Tests (TFT) were performed and showed significantly reduced Thyroid Stimulating Hormone (TSH) levels (< 0.02 uU/ml), elevated T3 (> 31.0 pmol/ml) and T4 (> 155 pmol/ml) levels. These levels and his symptoms indicated overt hyperthyroidism; with no previous history of thyroid problems. In addition, the Thyroglobulin (TG) level (2292 pmol/ml) and Thyroid Peroxidase Antibody (TPO-Ab) level (128 Iu/ml) were both significantly raised. The Sorafenib

treatment was ceased and carbimazole and propanalol given until his symptoms resolved after which the patient was re-commenced on Sorafenib again with close monitoring of his TFTs. As symptoms resolved, the carbimazole and propanolol were both ceased several weeks prior to his thyroid scan. The serial TFTs performed over the next 6 months are presented in Figure 1.

Figure 1

Fig1. Logarithmic values of TSH, T4 and T3 levels plotted with respect to time (a period of 6 months). It shows the initial hyperthyroid phase with increased levels of T4 and T3 with suppression of TSH. As the thyroiditis progressed, production of T4 and T3 starts to decrease. The negative feedback mechanism kicks in and TSH is produced. Towards the last 2 months, levels of T4 and T3 appears within the normal range but is inappropriate for the level of TSH. The patient at this stage has subclinical hypothyroidism.



A thyroid scan with Tc-99m Pertechnetate was performed 4 months after manifestation of symptoms (delays due to patient also having follow-up whole body CT scans) for further evaluation of the cause of this hyperthyroidism. There was no dominant autonomous nodule, the thyroid lobes were not enlarged or nodular and the uptake was within normal limits quantitatively (2.5%) and qualitatively (compared with the salivary glands). (Figures 2 & 3) An ultrasound of the thyroid was unremarkable.

Figure 2

Fig 2,3. Dynamic, Delayed and Uptake images shows a normal percentage uptake of 2.5% (normal 1 Â– 4%). Number of counts is appropriately more than the salivary glands. No dominant nodule or enlargement of the gland is demonstrated. Essentially a normal scan, until one correlates with the TFTs.

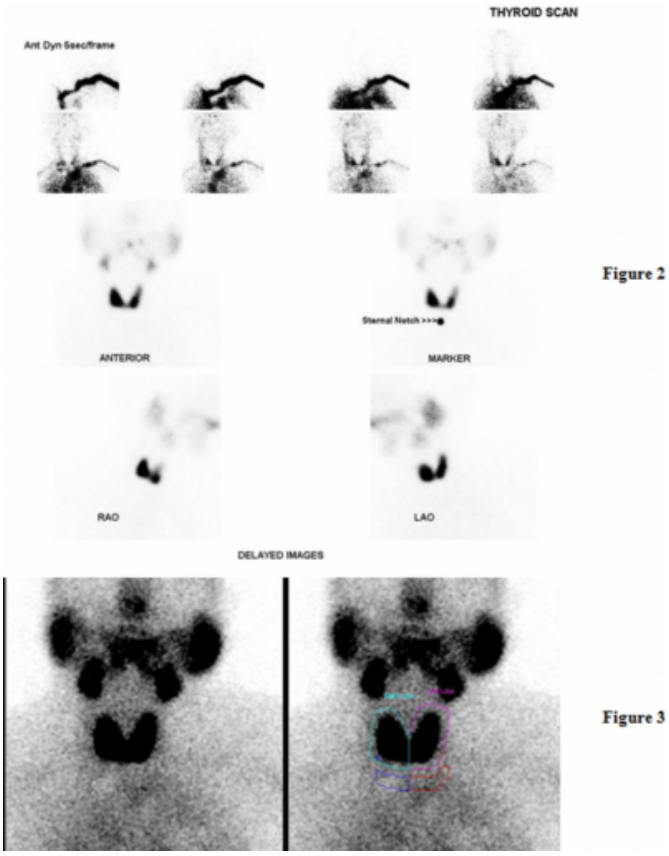


Figure 2

Figure 3

The TFTs showed an initial rise of T3 and T4 with gradual “normalisation”, and the TSH levels showed a steadily rising trend over the 6 months. Despite an interim iodine load (from contrast enhanced CT scan), T3 and T4 levels did not increase. The abnormal biochemical behaviour, the normal thyroid scan and the presence of TPO-Ab suggested an autoimmune thyroid reaction resulting in thyroid damage and release of T3 and T4. The thyroiditis has affected thyroxine production so that after the inital hyperthyroid phase, T3 and T4 levels dropped in spite of increased stimulation by elevated TSH. We conclude that hypothyroidism would ensue and thyroid replacement would be imminent. Given the temporal relation of initial hyperthyroidism within 4 months of starting Sorafenib treatment and lack of any intra-thyroidal structural lesion on the thyroid scan or ultrasound, we felt that this was indeed a case of drug induced painless thyroiditis.

DISCUSSION

The use of Sorafenib in the treatment of advanced HCC is relatively new. Side effects of the drug have been determined from its use in the treatment of mRCC in 3 other studies. These included Miyake et al in 2009 (69 patients)[2], Clement et al in 2008 (38 patients)[3] and Tamaskar et al in 2007 (39 patients)[4]. 5-18% of patients developed thyroiditis with subsequent hypothyroidism. The average time to onset of symptoms was 2-4 months after initiation of Sorafenib. Other patients suffered variable degrees of biochemical abnormalities with their TFTs. A separate study of Sunitinib, a similar Tyrosine Kinase Selective Inhibitor administered for gastrointestinal stromal tumours (GIST) and acute myeloid leukemia in 2007 by Mannavola et. al[5] demonstrated a high prevalence of hypothyroidism (46% of 24 patients) secondary to impaired iodine uptake from the drug. Advancing age[2], pre-existing underlying thyroid function abnormalities and concurrent radiotherapy to the neck[3] (for treatment of cervical spine bony metastases) increased the risk of thyroiditis post Sorafenib treatment. The mechanism of the induction of thyroiditis is not known, although the presence of TPO-Ab suggests an autoimmune response possibly brought about by molecular mimicry and bystander activation. The elevated level of thyroglobulin attests to the fact that there is thyroid follicular destruction. Correlation with the TFTs was highly useful in this case as it showed a clear trend of thyroiditis with an initial hyperthyroid phase followed by "normalisation" of T4 and T3 levels. With rising TSH levels, the inappropriately normal T4 and T3 values reflects the failing effort of the gland to compensate possibly due to follicular destruction.

The thyroid scan was helpful in that it excluded other causes of hyperthyroidism including Graves' disease where TPO-Ab can also be elevated, and Autonomous Toxic Nodules. In light of a raised TSH level (at the time the scan was performed), the normality of the thyroid scan was suspect. As the destruction of the thyroid gland progresses, intrathyroidal hormonogenesis is decreased. Pituitary TSH is released in response to decreased circulating levels of thyroid hormones that result from gland destruction. The TSH may stimulate the iodide trap in the remaining normal cells of the thyroid, and a high-normal radioiodine uptake may be seen. A new steady state condition is reached in which the TSH is high-normal and serum free T4 and T3 are supported at normal levels. Further progression of the destruction process eventually results in sufficient loss of thyrocytes to cause decreased and subnormal radioiodine uptake. It is highly likely the patient will imminently require thyroid hormone replacement.

In conclusion, TFTs monitoring should be performed in patients with risk factors for developing thyroiditis post Sorafenib treatment and when clinically indicated. This case highlights the fact that correlation of the thyroid scan with TFTs and the patient's symptoms is important and that the multidisciplinary interpretation of nuclear imaging with biochemical clinical parameters is vital for optimal scan interpretation, clinical diagnosis and management in patients being administered Tyrosine Kinase Inhibitors.

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