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CASE REPORT

A Case Report and Short Literature Review on Truncated Expression of the Na+/I- Symporter (TENIS) Syndrome in a Nigerian

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Summary

TENIS is an acronym for 'Truncated Expression of Na^+/I^- Symporter' or 'Thyroglobulin Elevation (but) Negative Iodine Scan'. Its diagnosis is made based on an incongruence between serum thyroglobulin levels and radioactive iodine imaging findings in patients with thyroid cancer. This report aims to present one of the earliest described patients with TENIS syndrome in Nigerian literature and to display the utility of basic nuclear medicine (NM) imaging in diagnosing the condition. This case report illustrates the clinical features of the syndrome with the typical clinical and imaging features of the TENIS syndrome: off-suppression serum thyroglobulin of 834 ng/ml in the presence of normal anti-thyroglobulin antibody levels. At the same time, the I-131 whole-body scan did not reveal a corresponding disease burden. It is concluded that improved NM and laboratory medicine services in the developing parts of the world are recommended to improve the detection and management of this syndrome.

Keywords: Iodine radioisotopes, Nuclear medicine, Radionuclide imaging, Symporter, Thyroglobulin, Thyroid neoplasms.

Introduction

Thyroid cancer is the most common endocrine tumour. Compared to its position as the eleventh most common cancer globally, in the year 2018, its incidence has increased almost 50% from 567,100 to 821,173, making it the seventh most common cancer in the year 2022. Regionally, the highest incidence was seen in West Asia (23 per 100,000), while West Africa had the lowest incidence (0.9 per 100,000). The sex ratio remains 1:3 in favour of women, in

whom it was the fifth most common cancer overall. [1–3]

The increased incidence has been attributed to disease over-detection. Over-detection, in turn, has been attributed to increased imaging, surveillance, and improved access to care. These are especially prominent in high-risk populations such as Japan. [4] Poorly differentiated thyroid cancer exhibits characteristics between the well-differentiated and anaplastic thyroid carcinomas. Patient presentation typically involves an older man with locoregional and possibly distant metastases. [5] Poorly differentiated thyroid carcinoma has a five-year survival rate of 50-85% and often demonstrates non-avidity for Radioactive Iodine (RAI) [6]

Radioisotope therapy with radioiodine-131 (RAI) is an adjuvant modality for treating well-differentiated thyroid cancer (DTC). This radioisotope is both a beta and a gamma-emitter. These properties make it suitable for therapy (beta particle emission) and imaging (gamma-ray emission). Radioactive iodine therapy (RAIT) for DTC has been divided into three main categories. The first category is treatment with RAIT for distant metastases or residual functioning DTC. [7] The second is adjuvant therapy for tumour-invading adjacent structures and organs, while the third is ablation of 'normal thyroid remnants'. [8]

Thyroglobulin (TG) is a sensitive tumour marker that monitors the course of differentiated thyroid cancer (DTC). As it is produced solely by thyroid tissue, it becomes a more specific tumour marker after total thyroidectomy and/or radioactive iodine (RAI) ablation. [9] This is because the elimination of native thyroid tissue or primary tumour limits the production of TG to metastases from DTC. [10] RAI imaging and therapy was commenced at the University College Hospital, Ibadan, 18 years before this research, treating patients with primary hyperthyroidism and DTC.

TENIS is an acronym for 'Truncated Expression of Na/I Symporter' (NIS). The crux of diagnosing the TENIS syndrome is the demonstration of an incongruence between TG and whole-body scans (WBS) using iodine-131. The diagnosis of the TENIS syndrome impacts further imaging and treatment of the affected patient, and is associated with worsened prognosis, as will be explained in greater detail. This report aims to increase awareness about the syndrome and highlight therapy options.

Case Description

A 60-year-old man presented at the University College Hospital, Ibadan, with metastatic poorly differentiated thyroid cancer (PDTC). He had cervical nodal and bilateral lung metastases which had been on RAI scans at another Nuclear Medicine Centre. He had also undergone RAI treatment there. A subsequent six-month WBS scan under endogenous thyroid-stimulating hormone (TSH) stimulation appeared free of metastases (Figure 1); however, his TG level was not in tandem and was elevated at 834 ng/ml, while the anti-TG antibody level remained within normal limits in concordance with the TENIS syndrome.

A subsequent Tc-99m sestamibi scan was unremarkable except for showed unusual focal right suprarenal uptake (Figure 2). Thereafter, a bone scan was performed; this revealed multiple axial osteoblastic lesions consistent with multiple skeletal metastases. The patient was then counselled regarding alternative management options as he would no longer benefit from RAIT; he opted to travel overseas for further treatment, as Positron Emission Tomography (PET) imaging was unavailable in Nigeria then.

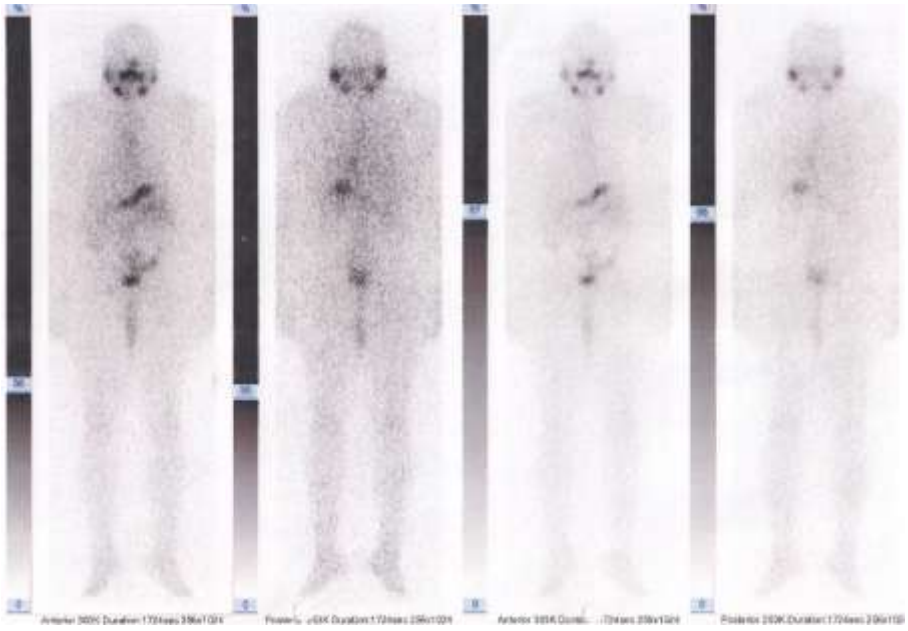

Figure 1: Anterior and posterior whole-body scan performed six months after the patient's previous RAI treatment under endogenous thyroid-stimulating hormone (TSH) stimulation appeared free of metastases. Normal distribution of radioactivity is seen showing secretion into the mouth and salivary glands, nasal region, stomach and bowel.

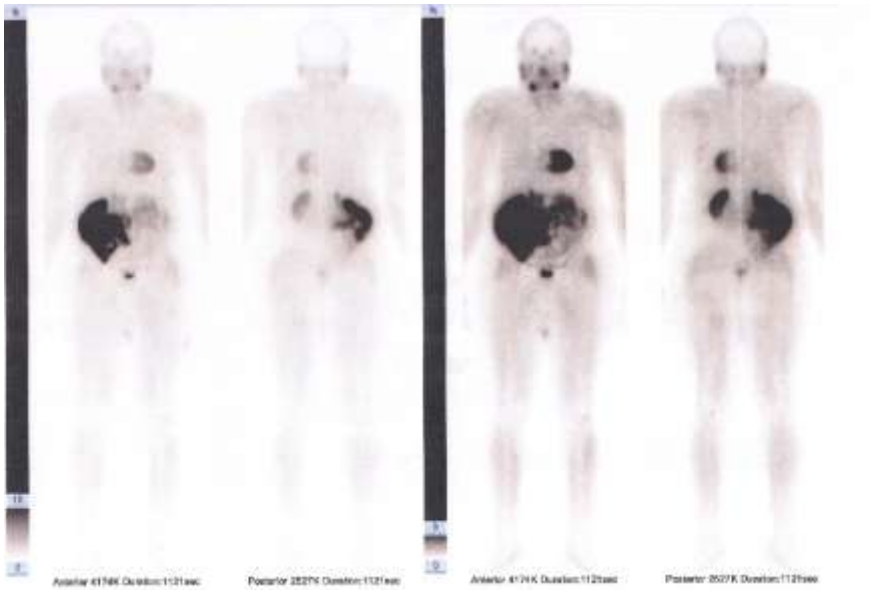

Figure 2: Anterior and posterior Tc-99m sestamibi planar images with unusual focal right suprarenal uptake which persisted on delayed imaging. Normal uptake and secretion of radioactivity is seen in myocardium, salivary glands, liver, intestines and urinary tract.

Literature review

Definition and aetiology of TENIS syndrome

Before diagnosing TENIS syndrome, variables to be considered include the degree of differentiation of thyroid cancer and the type of WBS performed (diagnostic ('low-dose) or therapeutic). [11] Other parameters to consider include the choice of radiotracer for imaging WBS (I-123 versus I-131), adequacy of patient

preparation for WBS, ATG antibodies causing falsely elevated TG, and nodal metastases. [12] Iodine-123 has better imaging qualities than I-131 but is less readily available for use in NM centres in developing countries. It has a half-life of 13 hours, making its importation less suitable than that of I-131, which has a half-life of eight days. Thus, some have considered using I-131 for WBS to be a contributor to false-negative WBS. [12] Nodal metastases might not be seen on WBS, presumably due to their size being below the resolution of the gamma camera. [12]

The aetiology of TENIS syndrome has been attributed to suboptimal TSH stimulation or poor patient preparation for WBS, resulting in suboptimal endogenous stimulation of thyroid tissue. Other possible aetiologies include dedifferentiation of DTC with dysfunctional NIS, the presence of heterophile anti-TG antibodies, histologically non-radioiodine-avid thyroid cancer, 'stunning' of thyroid tissue from diagnostic scans, and metastases being smaller than the detective ability or resolution of gamma camera. [13] Visualisation of cancer is also relatively poorer with diagnostic WBS compared to therapeutic scans. The index patient had poorly differentiated thyroid cancer, which initially displayed RAI-avidity but later did not.

Epidemiology of the TENIS syndrome

The prevalence of the syndrome has been quoted from a hospital-based study in Johannesburg, South Africa, as 2% from a population of 101 patients with papillary (55%), follicular (28%), Hürthle cell (8%), and 'mixed' thyroid cancer (9%). [14] Another hospital-based survey from Malaysia found a higher prevalence of 10%, with 85% of the cancers being papillary and the remainder being follicular. [15]

At the time of making this report, there was a paucity of literature about this pathology from Nigeria. While reports of the TENIS syndrome were not found in online literature from East and West Africa when presenting this case of interest, it is probable that the TENIS syndrome exists and has been underreported in those regions. Reports may also have been published in print journals without online versions.

Classification of the TENIS syndrome

Contrary to the broad description in clinical practice of reduced or absent uptake of RAI by thyroid cancer and metastatic deposits, the TENIS syndrome has multiple manifestations. First, metastatic DTC may not exhibit any uptake of RAI *ab initio*. In another variation, DTC may lose its ability to concentrate RAI after prior evidence of being RAI-avid. Furthermore, DTC may exhibit selective RAI uptake in some lesions but not in others. In addition, disease progression may occur despite significant RAI uptake. [7]

Clinical significance of TENIS syndrome/Prognosis

Patients affected by the TENIS syndrome have been deemed to be refractory or resistant to RAI uptake, implying RAI avidity, albeit of a quantity that is inadequate for imaging or treatment. However, thyroid cancer may also be non-RAI-avid, as is the case with most poorly differentiated and all anaplastic subtypes. [11] Patients diagnosed with the TENIS syndrome have a relatively poorer prognosis than other patients with DTC, with a dismal ten-year survival rate of 10%. [7] The prognosis improves, and RAIT may be utilised if metastases exhibit radioiodine avidity. A 'flip-flop' phenomenon exists whereby patients' prognosis worsens with F-18 fluorodeoxyglucose (F-18 FDG) positivity but RAI negativity. Low to non-existent iodine uptake in DTC is typically associated with increased glucose metabolism and positive FDG-PET scan results, whereas RAI positivity and FDG negativity improve patients' prognosis. [16,17] For instance, a small trial involving 40 patients with metastatic thyroid cancer and the TENIS syndrome demonstrated a better prognosis in those TENIS patients who had normal F-18 FDG PET/CT scans and elevated TG. [18,19]

Diagnosis of TENIS syndrome

From its definition, diagnosing TENIS syndrome requires the availability of serum TG and anti-TG assays and radioiodine imaging facilities. Diagnosing the TENIS syndrome also requires definitive histology of thyroid cancer, along with its variants. Imaging parameters such as collimators, energy windows, energy peaks, and SPECT/CT correlations must also be correctly set. The patients should also have been adequately prepared, with appropriate intervals between exposure to interfering medications/substances and scanning. The syndrome should be diagnosed after confirming adequate patient preparation and appropriate TSH stimulation of thyroid tissue. [7] Whole-body RAI scans and TSH, TG, and anti-TG antibody assays should always be interpreted together. Therefore, in countries where nuclear imaging and TG-detecting facilities are few or absent, cases of the TENIS syndrome may be underreported or undetected.

Management of the TENIS syndrome – Nuclear Medicine

Timely detection of the syndrome is of the utmost importance to alter the patient's management plan accordingly. Diagnosis must exclude confounders and pitfalls, as described above, to ascertain that the patient has the TENIS syndrome. Subsequent to a definitive diagnosis of TENIS syndrome, patient imaging should change from RAI to alternatives such as F-18 FDG, radiolabelled prostate-specific membrane antigen (PSMA), and neck ultrasonography.

Where FDG PET/CT is unavailable, imaging agents such as Tc-99m sestamibi may be used, as applied in the index patient. FDG positron-emission/computed tomography (PET/CT) and neck ultrasonography have also been recommended. The clinical suspicion of the TENIS syndrome may resolve with repeat WBS scans with higher quantities of radioactivity, and adequate patient preparation may reveal hitherto occult metastases.

In investigating PSMA for treating the TENIS syndrome, a small study presented findings from nine patients scanned with F-18 FDG and 68Ga-PSMA-HBED-CC PET/CT. PSMA imaging detected skeletal and lung lesions and relatively fewer lesions than FDG. Since PSMA uptake had been established as a therapeutic target, PSMA therapy could be attempted in these patients. [20]

The management of the syndrome depends on the stage of thyroid cancer. The locoregional spread could be treated by localised therapy such as lymph node clearance, surgical resection or metastectomy. Distant metastases could be treated by external beam radiotherapy, chemotherapy, bisphosphonate therapy for bone metastases, and molecular therapy. [21] The degree of FDG uptake also influences the treatment choice, as FDG-positive disease suggests aggressive disease. [12] Empirical RAI therapy for treating the TENIS syndrome has been fraught with controversies. [22] A survey of 288 members of the American Thyroid Association published in 2014 indicated that 15-61% of assessed members would opt for empirical RAI therapy. Most practitioners recommended RAI therapy with 75-150 mCi. [23] Empirical high-dose RAI therapy has been attempted to treat TENIS syndrome patients with varying results. While described as neither beneficial nor harmful, TG levels were reduced in other instances. At the same time, previously non-visualised lesions became visible on WBS in 17-57% of patients who had received such treatment.[24,25] Suppressed and stimulated serum TG levels decreased significantly (41% and 37%, respectively) in patients who opted for RAI (28/60) compared to untreated patients (32/60). [26] In yet another study, the effectiveness of RAI treatment in the TENIS syndrome was evaluated in a systematic review of 13 observational studies. The results showed that TG levels decreased after RAIT in 62% of patients. In addition, positive post-therapy scans were observed in 56% of these patients, suggesting a potential benefit. [27] If WBS shows

RAI uptake after empirical therapy and the serum TG level decreases, the patient may continue to benefit from further treatment with RAI. Patients in this latter group do not have the real TENIS syndrome. Prior non-visualisation of thyroid cancer in this group may have been due to the lower radioactivity administered for diagnostic WBS. [12]

Peptide receptor radionuclide therapy (PRRT) with Lu-177 DOTATE has been explored to treat metastatic TENIS with encouraging results. Patients who responded to Y-90-DOTA-TOC in a clinical trial lived thrice as long as those who did not. Initial diagnostic somatostatin receptor (SSTR) imaging should precede PRRT so that only patients with high avidity for the peptide receptor analogue are selected for treatment. [28]

Management of the TENIS syndrome – other modalities

Attempts at treating the syndrome with doxorubicin resulted in a dismal partial response (less than 10%), progressive disease in half of them, and stable disease in 42% over an 11-month follow-up. [29] Similarly, chemotherapy with gemcitabine and oxaliplatin in 14 patients resulted in a complete response of 7%, a partial response of half of the patients, and a stable disease of 28%. [30] External beam radiation therapy for metastatic TENIS syndrome will provide symptomatic relief and to offer palliation. [31] It also offers longer disease-free progression. EBRT is also preferred to RAIT in treating brain lesions on account of the resulting oedema from RAIT. [32]

Molecular therapy of TENIS syndrome involves tyrosine kinase inhibitors (TKIs), a targeted cancer therapy. Their mechanism of action consists of blocking receptors of tyrosine kinase enzymes, which are involved in the development and continuance of tumours. [33] Sorafenib and lentinib are first-line systemic treatment choices for the TENIS syndrome. Both drugs have common therapy targets - vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), as well as Rearranged during Transection (RET) and c-kit proto-oncogenes. In addition, lenvatinib inhibits the actions of vascular endothelial growth factor receptor-4 (VEGFR-4) and fibroblast growth factor receptor (FGFR). [34]

Lenvatinib is indicated for the treatment of the TENIS syndrome in patients with progressive disease, either local, recurrence or metastatic. [33] Two phase III trials comparing lenvatinib or sorafenib versus placebo have shown prolongation of progression-free survival (PFS) and overall response in patients with the TENIS syndrome. Patients treated with sorafenib had twice the PFS experienced by patients on placebos, while PFS in patients on lenvatinib therapy was six times higher than in those on placebo. [35,36] Lenvatinib also produced a significant PFS advantage in the Phase 3 trial of the Study of E7080 Lenvatinib in Differentiated Cancer of the Thyroid (SELECT study) compared to a placebo. [33] In yet another study, eight patients with poorly differentiated (2/8) and anaplastic carcinoma (6/8) were treated with a combination of lenvatinib and pembrolizumab. All had failed prior therapy with surgery, radiation therapy or RAI. The patients were followed up for up to 40 months. The median PFS was approximately 18 months, and the median overall survival rate was slightly higher at 19 months. [37]

Conclusion

Despite the limited NM and laboratory resources available in this Nigerian centre, these were adequate to diagnose the TENIS syndrome. The provision of improved NM and laboratory medicine services in this region is recommended to improve the detection and management of this syndrome.

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Authors' Contributions: OYA conceived the research, performed the literature searches, drafted the manuscript, and revised it for sound intellectual content.

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