

DEEPENDRA KASAUDHAN
PRASHANT TRIPATHI
KUNJAN ACHARYA

Ganesh Man Singh Memorial Academy
of ENT and Head & Neck Studies
TU Teaching Hospital
Kathmandu, Nepal

Corresponding Author:

Dr. Deependra Kasaudhan

Ganesh Man Singh Memorial Academy
of ENT and Head & Neck Studies
TU Teaching Hospital
Kathmandu, Nepal
Email: here2sharewith@gmail.com

THYROGLOBULIN-ELEVATION NEGATIVE IODINE SCINTIGRAPHY (TENIS) SYNDROME IN DIFFERENTIATED THYROID CARCINOMA: A RARE ENTITY

ABSTRACT

Differentiated thyroid cancer (DTC) patients with Thyroglobulin Elevation but Negative Iodine Scintigraphy, the 'TENIS' syndrome, represent a diagnostic and therapeutic challenge. Routine follow up of patients with DTC after operation is usually done with serum TSH and thyroglobulin levels (Tg). Elevated thyroglobulin levels alarms a need for search for metastatic foci or remnant disease which are sometimes missed with radioiodine thyroid scan in cases of radioiodine non-avid thyroid cancers. 18 Fluoro-2-deoxyglucose Positron Emission Tomography (18FDG-PET) scan is a useful alternative to trace the metastatic foci of tumor or nodal deposits in such cases. Management, thus, can be tailored accordingly. If isolated metastatic foci is traced, it has to be resected prior to radioiodine ablation with a follow up scan and Tg determination.

Keywords: Differentiated thyroid cancer(DTC), ¹⁸ FDG-PET scan, TENIS syndrome

INTRODUCTION

Papillary carcinoma accounts for 75-80% of thyroid malignancies.¹ Surgery remains the mainstay of management in Differentiated Thyroid Cancer (DTC). Thyroglobulin-elevation, negative iodine scintigraphy (TENIS) syndrome is an uncommon scenario in the follow up of patients with differentiated thyroid cancers after surgical modality of treatment has been offered. Of the variety of imaging studies used to investigate patients with elevated thyroglobulin levels following treatment for DTC, 18 Fluoro-2-deoxyglucose Positron Emission Tomography (18FDG-PET) CT scanning appears to be the most sensitive test.¹ The sensitivity in detecting metastases in DTC increases with increasing thyroglobulin levels.² Following total thyroidectomy and radioactive iodine ablation, serial thyroglobulin measurement is more sensitive test than lowdose¹³¹I scan.^{3,4} It has the potential to miss large numbers of foci of recurrent disease in all risk groups but there is a particular concern in older patients in whom DTC has a lower avidity for radioactive iodine⁵ and in whom there is a higher risk of nodal disease and recurrence and a worse prognosis.² Routine ¹³¹I whole body scanning post-ablation is being abandoned in low risk patients since the majority will have negative scans and serum thyroglobulin is a more sensitive, accurate investigative and monitoring tool.⁶

Usually, false-negative scan could be due to two

reasons: (a) volume of disease below the sensitivity level of the imaging modality or (b) thyroid cancer cells which are non-iodine avid, dedifferentiated or of Hurthle cell type and are unable to take up radioiodine.⁷

Studies have shown that in patients with elevated serum Tg levels and a negative diagnostic radioactive iodine whole body scan, FDG-PET CT scans can demonstrate disease that is amenable to surgery and can lead to disease-free status in a significant number of patients.⁸ In addition, FDG-PET CT scanning appears particularly useful in tumours that do not concentrate radioactive iodine where radioiodine scanning is not at all useful and where metastases have a poorer prognosis.³

CASE REPORT

A 33 years old male was referred to visit ENT Out-patient Department (OPD), TUTH. He had history of total thyroidectomy with central compartment neck dissection (CCND) done for papillary thyroid carcinoma (T3N1M0) with post-operative radioiodine thyroid ablation 15 months back and was on regular follow up with serum Thyroid Stimulating hormone (TSH) and serum thyroglobulin levels. Patient was on regular thyroxine replacement 175 microgram/day after operation. The case was referred to our centre after thyroglobulin level was elevated (222 ng/ml) with negative thyroid scan (Fig. 1) and USG neck

revealed approx. 1.4 x 0.7 cm left level IV lymph node during follow-up. USG-guided FNAC from same node revealed features suggestive of metastatic papillary carcinoma. Following which whole body radioiodine (^{131}I) thyroid scan was done which turned out to be negative. MRI neck showed features suggestive of left Level IV lymphadenopathy. After this, FDG-PET CT scan was advised which showed FDG-avid left Level IV lymph node suspicious for metastasis and FDG-avid subcarinal and hilar lymphadenopathy. Endobronchial Ultrasound (EBUS) revealed heterogenous subcarinal node (size 22.2x12.5 mm) with no calcification and no coagulation necrosis. Transbronchial Needle Aspiration (TBNA) from subcarinal lymph nodes showed no evidence of malignancy.

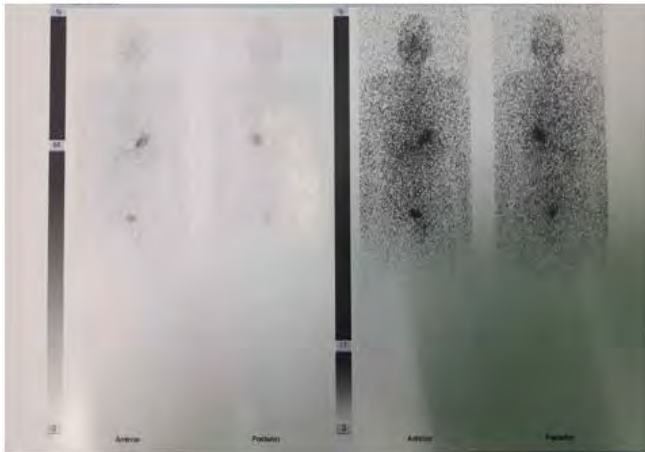


Fig.1 Thyroid scan –No uptake at thyroid bed

Finally, he was diagnosed as post-operated case of total thyroidectomy with CCND with neck metastasis (Left Level IV lymph node) and was planned for Left selective neck dissection (Level II-V). Routine pre-operative investigations were within normal limits. T3 and T4 levels were within normal limit with suppressed TSH (0.016 $\mu\text{IU}/\text{ml}$). He underwent left selective neck dissection (Level II-V). He had fibrofatty tissue along with left level IIa, IIb, III, IV, V lymph nodes removed. Left spinal accessory nerve (SAN) identified and preserved and left external jugular vein (EJV) ligated.

Postoperative histopathology report showed six out of 29 lymph nodes from level II and III with evidence of metastatic papillary carcinoma, lymph nodes from level IIB, Level IV and Level V lymph nodes free of tumor. On three months post operative follow-up, thyroglobulin (TG) level was 7.25ng/ml (N<55ng/ml) and Anti-thyroglobulin (Anti-TG) was negative.

DISCUSSION

Differentiated thyroid cancer (DTC) patients with Thyroglobulin Elevation but Negative Iodine Scintigraphy, the 'TENIS' syndrome, represent a diagnostic and therapeutic challenge. The discussed causes of TENIS syndrome presentation in DTC are anti-Tg antibody, microscopic remnants of normal tissue or of metastatic disease not visible with the diagnostic activity of ^{131}I , inadequate serum TSH stimulation, macroscopic metastatic disease that has mutated to lose sodium-iodide symporter (NIS), or a combination of these factors.⁹

Among epidemiological, pathological and clinical characteristics, lymph node, and locoregional invasion are the most frequently found parameter in patients with a DTC with high thyroglobulin (Tg) level and negative iodine scintigraphy.¹⁰ A good knowledge of these factors and causes of TENIS syndrome are required to ensure better management of patients. FDG-PET CT scan is the most sensitive test in such regards.^{1,10} After recurrent or metastatic disease has been traced via FDG-PET scan, further modality of treatment can be sought for. ^{18}F FDG PET/CT scan had higher sensitivity in patient with thyroglobulin higher than 4.6 mg/ml.¹¹ The physician must decide at what level of serum thyroglobulin (Tg) further investigation is necessary. The American Thyroid Association guidelines suggest level of stimulated Tg 2 ng/ml as a diagnostic threshold. Most current evidence suggests that patients with papillary or follicular thyroid cancer after total thyroidectomy who are Tg positive (Tg ≥ 10 ng/ml) and radioactive iodine scan negative warrant treatment with 100 mCi of ^{131}I with a follow up scan and Tg determination. If isolated focal metastatic deposits are present they should be resected before treatment with radioiodine.¹² In our case as well, focal metastatic deposit found at left level IV lymph node was removed via selective neck dissection and patient is advised to follow up with thyroglobulin level every three months.

CONCLUSION

Thyroglobulin Elevation but Negative Iodine Scintigraphy, the 'TENIS' syndrome, is a rare entity seen in cases of follow up of patients with differentiated thyroid cancer. Often focal metastatic deposits after surgery are missed with routine thyroid scan during follow up. ^{18}F FDG-PET scan proves to be the best alternative in such regards to locate the metastatic foci which has led to increasing thyroglobulin levels despite negative thyroid scan.

REFERENCES

1. Lind P, Kohlfürst S. Respective Roles of Thyroglobulin, Radioiodine Imaging, and Positron Emission Tomography in the Assessment of Thyroid Cancer. *Seminars in Nuclear Medicine*. 2006;36(3):194-205.
2. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World journal of surgery*. 1994;18(4):559-67.
3. Mazzaferri EL. Empirically treating high serum thyroglobulin levels. *The Journal of Nuclear Medicine*. 2005;46(7):1079.
4. Mazzaferri EL, Robbins RJ, Spencer C, Braverman L, Pacini F, Wartofsky L, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *The Journal of Clinical Endocrinology & Metabolism*. 2003;88(4):1433-41.
5. Schlumberger M, Challeton C, De Vathaire F, Travagli J-P. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *The Journal of Nuclear Medicine*. 1996;37(4):598.
6. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19(11):1167-214.
7. Moss L. *Stell and Maran's Textbook of Head and Neck surgery and Oncology-5th edition*. 2012;volume 1:494-509.
8. Helal BO, Merlet P, Toubert M-E, Franc B, Schwartz C, Gauthier-Koelesnikov H, et al. Clinical impact of 18F-FDG PET in thyroid carcinoma patients with elevated thyroglobulin levels and negative 131I scanning results after therapy. *Journal of Nuclear Medicine*. 2001;42(10):1464-9.
9. Silberstein EB. The Problem of the Patient with Thyroglobulin Elevation but Negative Iodine Scintigraphy: The TENIS Syndrome. *Seminars in Nuclear Medicine*. 2011;41(2):113-20.
10. Sfar R, Kamoun T, Noura M, Regaieg H, Ammar N, Charfi H et al. Differentiated thyroid cancer with thyroglobulin elevation and negative iodine scintigraphy (TENIS syndrome). *International Journal of otolaryngology and head and neck surgery*. 2014;3:149-153.
11. Giovanella L, Ceriani L, De Palma D, Suriano S, Castellani M, Verburg FA. Relationship between serum thyroglobulin and 18FDG-PET/CT in 131I-negative differentiated thyroid carcinomas. *Head & Neck*. 2012;34(5):626-31.
12. Clark Oh, Hoelting T. Management of Patients with Differentiated Thyroid Cancer Who Have Positive Serum Thyroglobulin Levels and Negative Radioiodine Scans. *Thyroid*. 1994;4(4):501-5.

