Immunotherapy in Radioactive Iodine Refractory Thyroid Cancer – Case Report and Review of Literature

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ABSTRACT

The therapeutic approach to radioiodine-refractory advanced differentiated thyroid cancer has undergone significant advancements in recent years, leading to a paradigm shift in its management protocol. Despite being recognized for its favorable prognosis, 15–25% of cases continue to defy conventional treatment. In recent times, cancer immunotherapy has been revolutionized by the approval of immune checkpoint blockade therapies, including anti-angiogenic multi-kinase inhibitors and fusion-specific kinase inhibitors. However, none of these treatments are curative, and most patients eventually show disease progression. Therefore, contemporary research is now focused on detecting resistance mechanisms to these agents.

This case report discusses the progression of a radioiodine-refractory advanced DTC patient who received conventional management followed by two multi-kinase inhibitors, Lenvatinib and Cabozanitib. Consequently, the prognosis was assessed using biochemical, genetic, and clinical findings.

Keywords: radioiodine refractory thyroid cancer, immune checkpoint blockade, multi-kinase inhibitors.

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CASE REPORT

In late 2018, a 68-year-old woman reported a swelling in front of the neck with nodular sensation along the left side of the neck. A diagnostic ultrasound was requested, which revealed a solid nodule with microcalcification in the left thyroid lobe as well as left anterior cervical lymphadenopathy with a grossly altered architecture. Fine-needle aspiration was suggestive of papillary thyroid carcinoma, with evidence of metastasis to the left anterior cervical lymph nodes (levels II, V, and VI). Eventually, the patient underwent total thyroidectomy with modified radical neck dissection type-1 on the left and comprehensive neck dissection on the right. Per-operative findings were significant for adherence of the tumor to the left carotid artery and left internal jugular vein (IJV); hence, the left sternocleidomastoid and IJV were sacrificed. The post-operative histopathology report revealed papillary carcinoma with bilateral metastasis to cervical lymph nodes (9 on the left and 3 on the right) with a staging of pT3N2Mx. She was initially treated with 150 mCi of radioactive iodine in early 2019. Her post-therapy scan showed a single focus of radiotracer concentration in the thyroid bed. She was initiated on levothyroxine replacement therapy and advised to follow up.

Her regular follow-up visits, which comprised estimation of thyroglobulin, anti-thyroglobulin antibodies, and ultrasound of the neck, revealed evidence of structural disease on both sides of the anterior cervical chain as well as a persistently elevated thyroglobulin level. For her further management, she was planned for a second surgery.

Eventually, excision of a recurrent left neck mass was performed in mid-2022, which showed a large neck mass with about 240° encircling adhesion to the left carotid artery and two other masses near the manubrium sterni. Additionally, her post-operative CT scan revealed irregular enhancing soft tissue mass (28x21x20 mm) in the thyroid bed in the upper pre-tracheal region and bilateral extensive pulmonary and right pleural metastasis. Following that, she received her second radioactive iodine therapy with 150 mCi in late 2022.

Nevertheless, despite receiving radioactive therapy twice, disease progression was evident. Her thyroglobulin level continued to remain elevated, and a further high-resolution CT scan revealed irregular enhancing lower pretracheal mass (24x19x18 mm), pulmonary and pleural metastasis, and an irregular

myocardial wall of the right atrium with diffuse pericardial thickening. Moreover, histopathology of tissue from the neck mass showed papillary adenocarcinoma of the thyroid. Despite that, her radioactive iodine whole-body scan showed no focal or diffuse radiotracer uptake anywhere in the body.

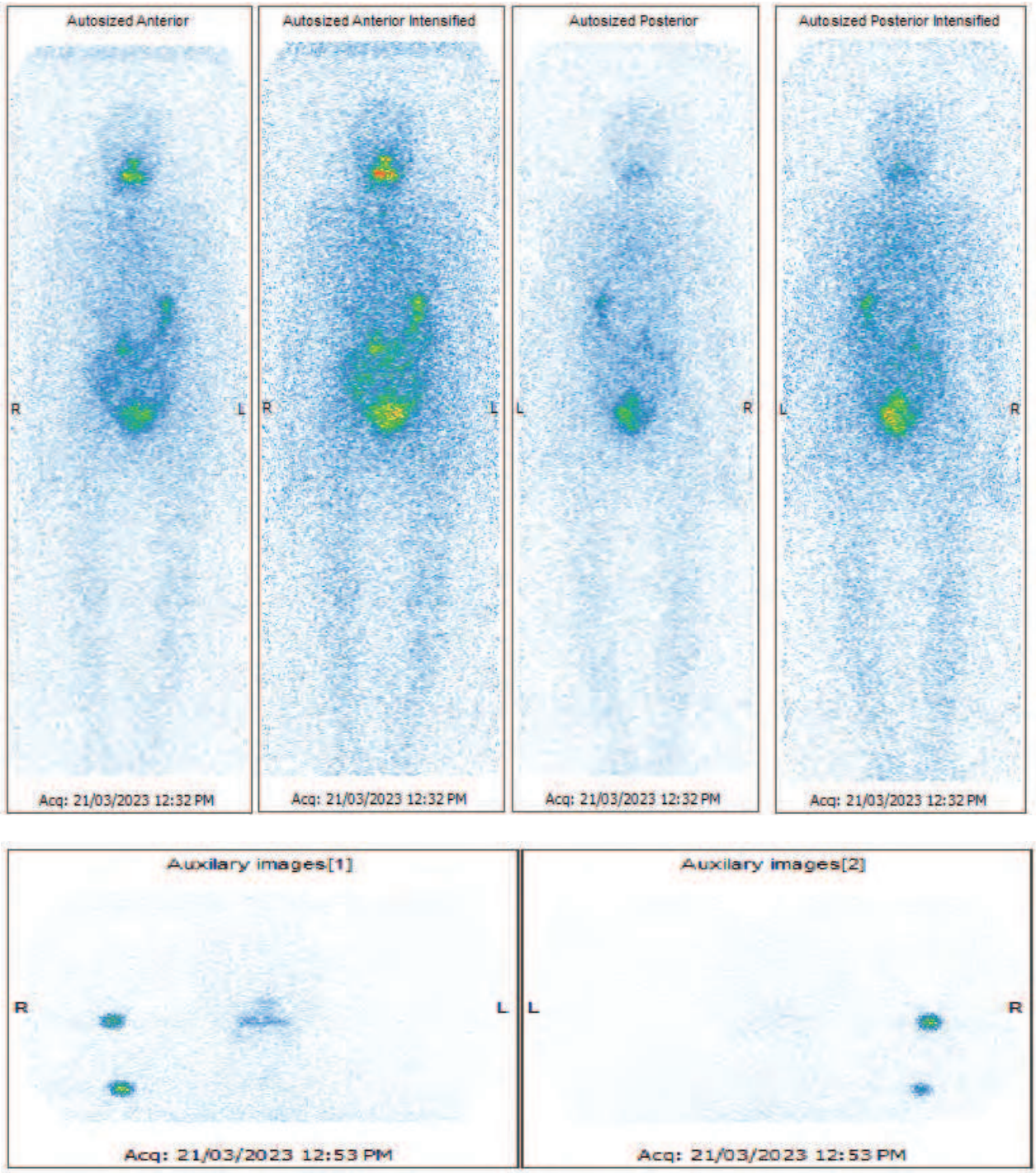
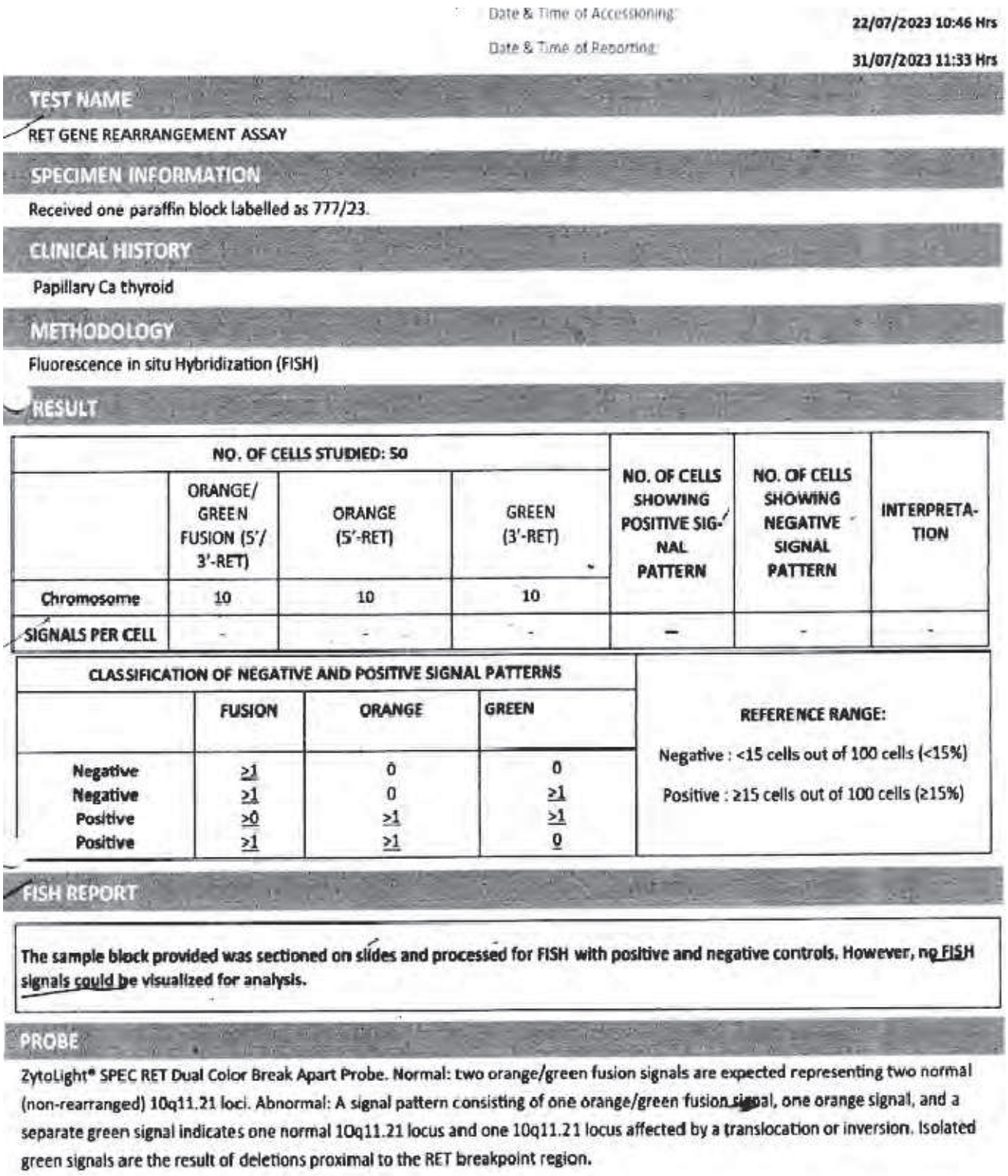


Figure 1: Post therapy whole body scan image of a 68-year-old woman of differentiated thyroid carcinoma, showing no abnormal radiotracer concentration after 2nd RAI therapy with 150mCi ^{131}I

Her RET gene rearrangement assay was processed for Fluorescence in situ Hybridization (FISH); however, no FISH signals could be visualized for analysis.



Date & Time of Accessioning: 22/07/2023 10:46 Hrs

Date & Time of Reporting: 31/07/2023 11:33 Hrs

TEST NAME

RET GENE REARRANGEMENT ASSAY

SPECIMEN INFORMATION

Received one paraffin block labelled as 777/23.

CLINICAL HISTORY

Papillary Ca thyroid

METHODOLOGY

Fluorescence in situ Hybridization (FISH)

RESULT

NO. OF CELLS STUDIED: 50				NO. OF CELLS SHOWING POSITIVE SIGNAL PATTERN	NO. OF CELLS SHOWING NEGATIVE SIGNAL PATTERN	INTERPRETATION
	ORANGE/ GREEN FUSION (5'/ 3'-RET)	ORANGE (5'-RET)	GREEN (3'-RET)			
Chromosome	10	10	10			
SIGNALS PER CELL	-	-	-	-	-	-

CLASSIFICATION OF NEGATIVE AND POSITIVE SIGNAL PATTERNS			
	FUSION	ORANGE	GREEN
Negative	≥1	0	0
Negative	≥1	0	≥1
Positive	>0	≥1	≥1
Positive	≥1	≥1	0

REFERENCE RANGE:

Negative : <15 cells out of 100 cells (<15%)

Positive : ≥15 cells out of 100 cells (≥15%)

FISH REPORT

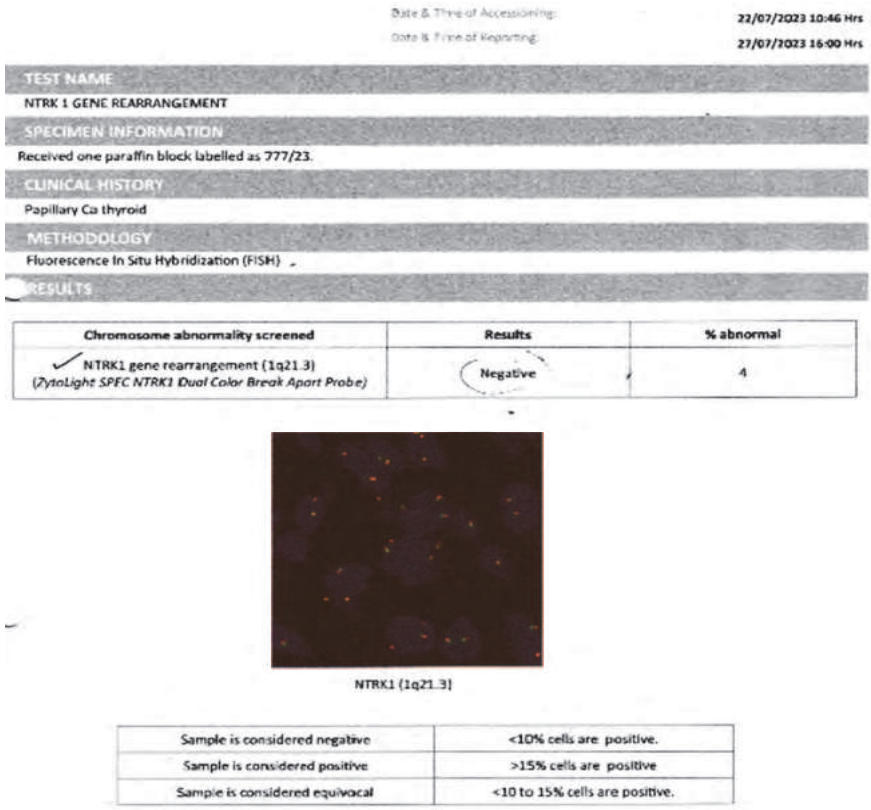
The sample block provided was sectioned on slides and processed for FISH with positive and negative controls. However, no FISH signals could be visualized for analysis.

PROBE

ZytoLight® SPEC RET Dual Color Break Apart Probe. Normal: two orange/green fusion signals are expected representing two normal (non-rearranged) 10q11.21 loci. Abnormal: A signal pattern consisting of one orange/green fusion signal, one orange signal, and a separate green signal indicates one normal 10q11.21 locus and one 10q11.21 locus affected by a translocation or inversion. Isolated green signals are the result of deletions proximal to the RET breakpoint region.

Figure 2: RET gene rearrangement assay by FISH (Fluorescence in situ Hybridization), howing no FISH signals, indicating a negative test result

Similarly, NTRK 1 gene arrangement (1q21.3) turned out to be negative with only 4% cells being abnormal (>15% abnormal cells are considered positive).



Date & Time of Accessioning: 22/07/2023 10:46 Hrs
Date & Time of Reporting: 27/07/2023 16:00 Hrs

TEST NAME
NTRK 1 GENE REARRANGEMENT

SPECIMEN INFORMATION
Received one paraffin block labelled as 777/23.

CLINICAL HISTORY
Papillary Ca thyroid

METHODOLOGY
Fluorescence In Situ Hybridization (FISH)

RESULTS

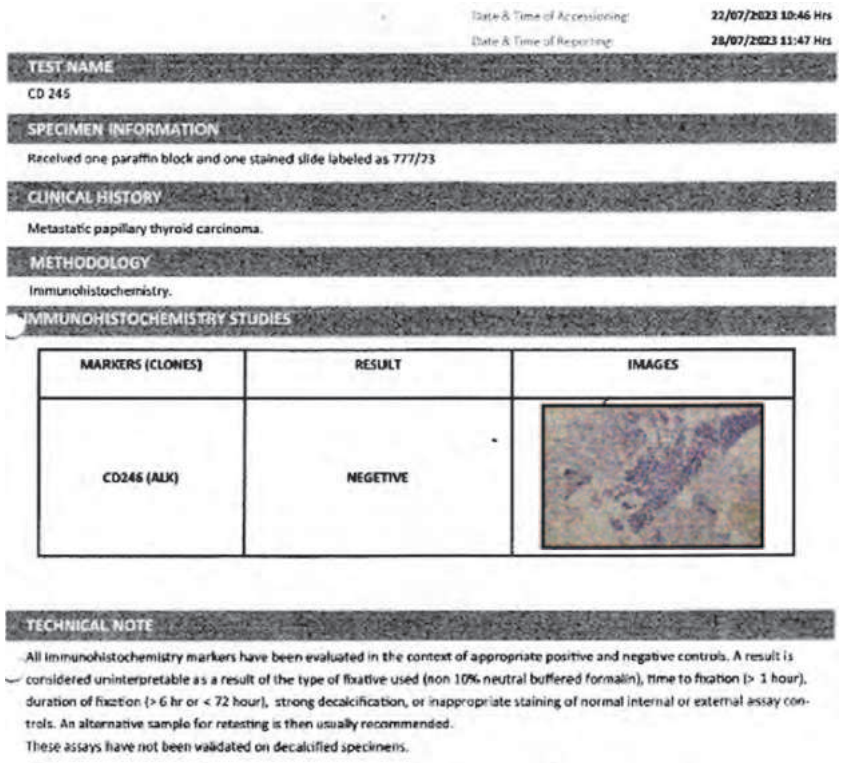
Chromosome abnormality screened	Results	% abnormal
✓ NTRK1 gene rearrangement (1q21.3) (*ZytoLight SPEC NTRK1 Dual Color Break Apart Probe*)	Negative	4

NTRK1 (1q21.3)

Sample is considered negative	<10% cells are positive.
Sample is considered positive	>15% cells are positive
Sample is considered equivocal	<10 to 15% cells are positive.

Figure 3: NTRK 1 gene arrangement by FISH method, showing only 4% abnormal cells.

On immunohistochemistry, her CD246 (ALK) marker was found to be negative as well.



Date & Time of Accessioning: 22/07/2023 10:46 Hrs
Date & Time of Reporting: 28/07/2023 11:47 Hrs

TEST NAME
CD 246

SPECIMEN INFORMATION
Received one paraffin block and one stained slide labeled as 777/23

CLINICAL HISTORY
Metastatic papillary thyroid carcinoma.

METHODOLOGY
Immunohistochemistry.

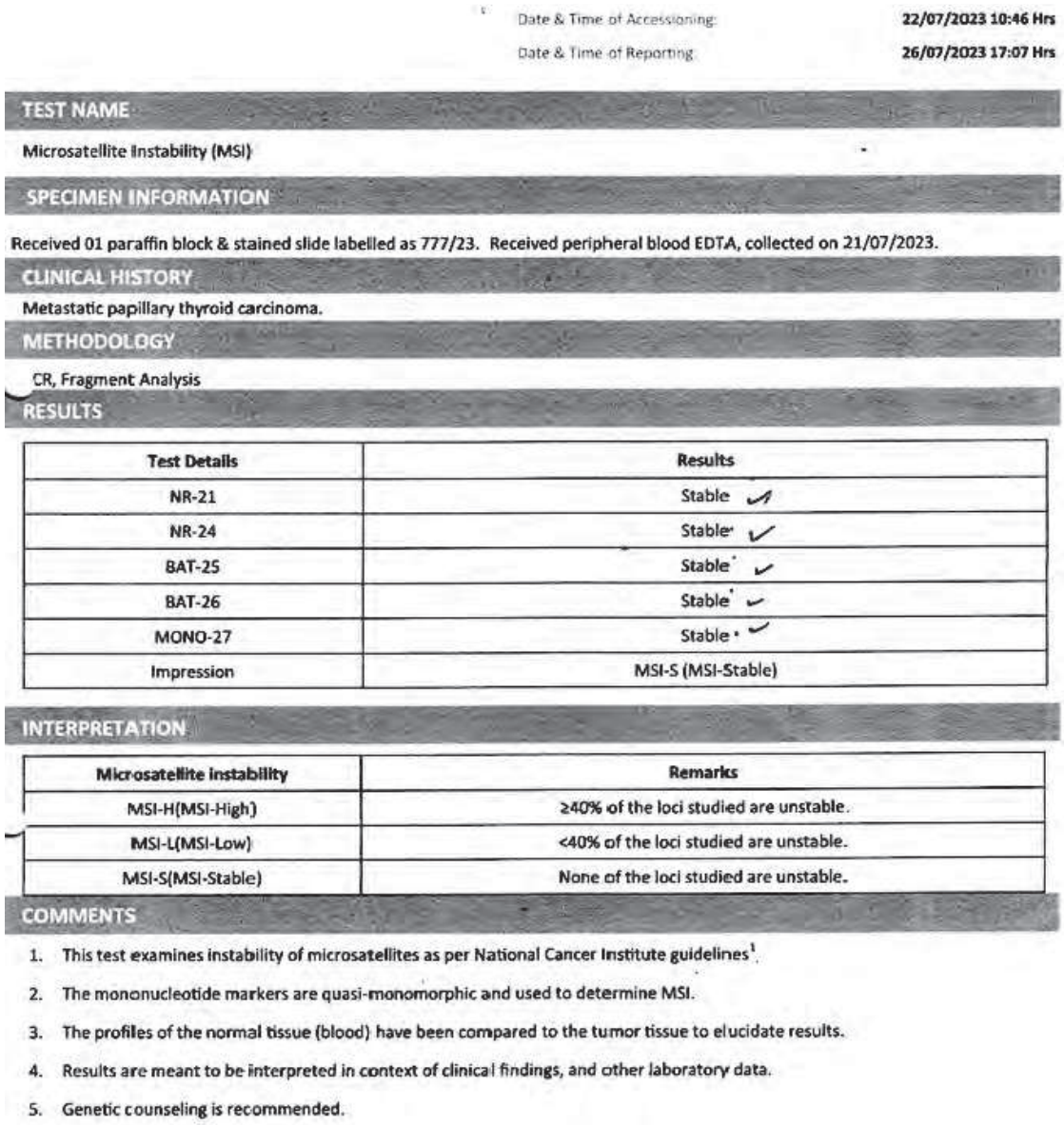
IMMUNOHISTOCHEMISTRY STUDIES

MARKERS (CLONES)	RESULT	IMAGES
CD246 (ALK)	NEGETIVE	

TECHNICAL NOTE
All immunohistochemistry markers have been evaluated in the context of appropriate positive and negative controls. A result is considered uninterpretable as a result of the type of fixative used (non 10% neutral buffered formalin), time to fixation (> 1 hour), duration of fixation (> 6 hr or < 72 hour), strong decalcification, or inappropriate staining of normal internal or external assay controls. An alternative sample for retesting is then usually recommended.
These assays have not been validated on decalcified specimens.

Figure 4: Immunohistochemistry of CD246 (ALK) marker, shows negative findings.

PCR, Fragment analysis for Microsattelite instability (MSI), which is a sign of DNA mismatch repair (MMR) deficiency and presents as accumulation of mutations in DNA microsattelite (1-9 nucleotides), was stable with absence of any unstable loci.



Date & Time of Accessioning: 22/07/2023 10:46 Hrs
Date & Time of Reporting: 26/07/2023 17:07 Hrs

TEST NAME

Microsatellite Instability (MSI)

SPECIMEN INFORMATION

Received 01 paraffin block & stained slide labelled as 777/23. Received peripheral blood EDTA, collected on 21/07/2023.

CLINICAL HISTORY

Metastatic papillary thyroid carcinoma.

METHODOLOGY

CR, Fragment Analysis

RESULTS

Test Details	Results
NR-21	Stable
NR-24	Stable
BAT-25	Stable
BAT-26	Stable
MONO-27	Stable
Impression	MSI-S (MSI-Stable)

INTERPRETATION

Microsatellite instability	Remarks
MSI-H(MSI-High)	≥40% of the loci studied are unstable.
MSI-L(MSI-Low)	<40% of the loci studied are unstable.
MSI-S(MSI-Stable)	None of the loci studied are unstable.

COMMENTS

1. This test examines instability of microsatellites as per National Cancer Institute guidelines[1].
2. The mononucleotide markers are quasi-monomorphic and used to determine MSI.
3. The profiles of the normal tissue (blood) have been compared to the tumor tissue to elucidate results.
4. Results are meant to be interpreted in context of clinical findings, and other laboratory data.
5. Genetic counseling is recommended.

Figure 5: Microsattelite instability (MSI)-S (Stable) was revealed following PCR.

In accordance with the negative findings of ALK, NTRK, and RET gene rearrangements and MSI results, the patient was first commenced on Lenvatinib in June 2023, which she continued for 3 months. Her biochemical findings, including a full blood count, hepatic enzymes, and renal function tests, were within normal limits at the start of treatment. After 3 months of treatment, a follow-up CT scan of the chest was done, which revealed further progression of the disease, characterized by numerous bilateral pulmonary lesions, with the largest one measuring about 4.2 x 2.7 cm. Consequently, a medical board comprising oncologists and internists was established in December 2023, and the patient's medical history was thoroughly reviewed. The board recommended discontinuing Lenvatinib and beginning Cabozanitib instead.

In January 2024, a repeated radioactive iodine whole body scan was conducted, and the results were consistent with the previous scan, indicating the absence of any abnormal focal or diffuse radiotracer uptake anywhere in the body. The patient was recommended to undergo a PET CT scan, but due to her poor physical condition, she was unable to comply. The patient is currently on Cabozanitib and has been scheduled for routine follow-up.

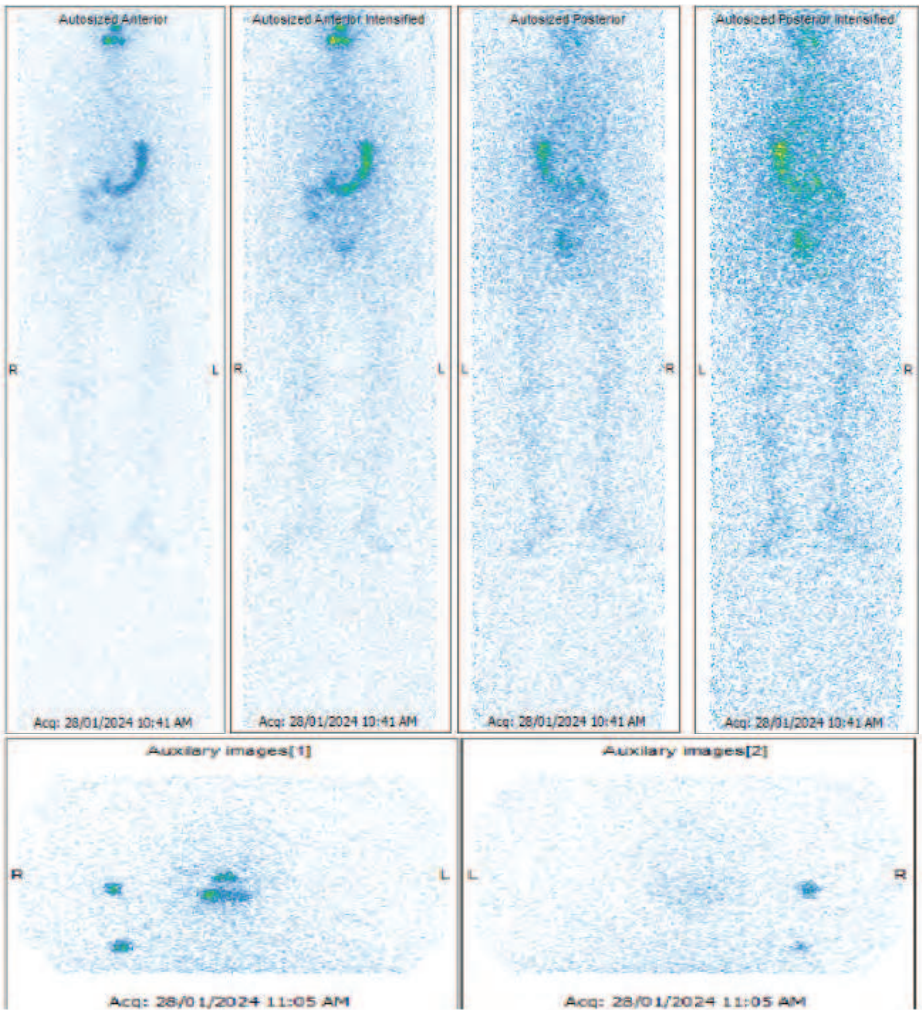


Figure 6: Follow-up ^{131}I-Whole Body Scan, after treatment with Lenvatinib, showing no abnormal radiotracer accumulation anywhere in the body, apart from physiological uptake in the salivary glands, bowel & urinary bladder.

DISCUSSION

The 2015 American Thyroid Association Management Guidelines suggested the following criteria as the definition of structurally evident radioiodine-refractory DTCs: (i) Metastatic tissue does not concentrate radioiodine; (ii) tumour tissue loses the ability to concentrate radioactive iodine after previous evidence of radioiodine-avid disease; (iii) radioiodine is concentrated in some lesions but not in others; and (iv) metastatic disease progresses despite a significant concentration of radioiodine (3). Recent advancements in the study of the genetic basis of papillary thyroid cancer demonstrated that the BRAF V600E mutation accounts for 60%, RAS for 15%, and receptor tyrosine kinase (RTK) accounts for 12% of these refractory cases (4).

Radioiodine refractoriness is mainly related to the sodium iodide symporter (NIS) expression of thyroid cancer cells (5). RTK and MAPK pathways are crucial for thyroid-specific gene expression, including NIS. Radioiodine refractoriness is linked to MAPK pathway activation (6).

Disease-specific therapies block the MAPK pathway in thyroid cancers, but their effectiveness in improving overall survival is questionable due to factors like parallel signaling pathway activation and overexpression of certain tyrosine kinase receptors, which ultimately affect treatment responses (7).

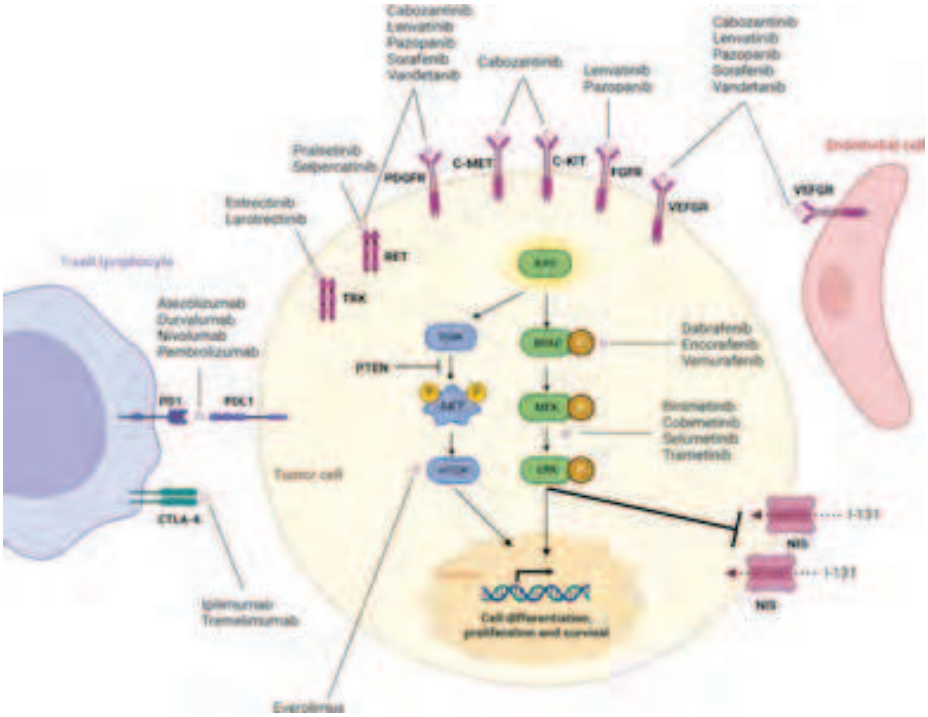


Figure 7: Pathway blocking actions of different targeted therapy agents.

In this case, initially the patient expressed radioiodine avidity and received radioiodine therapy twice thereafter. Despite that, further progression of the disease was noted, with a significant decline in radioactivity over time. Following RET, NTRK1 gene rearrangement, and MSI studies, Lenvatinib was prescribed. Regardless of the treatment, disease progression was obvious, in association with potential adverse events. The patient is currently being evaluated carefully and scheduled for ^{18}F-FDG PET/CT.

The National Comprehensive Cancer Network® (NCCN®) has released Clinical Practice Guidelines for Thyroid Carcinoma, recommending multi-kinase inhibitors for treating recurrent, advanced, and metastatic disease not amenable to radioactive iodine therapy. These include Lenvatinib or Sorafenib as first-line drugs, Cabozanitib as second-line therapy, Larotrectinib or Entrectinib for positive NTRK gene fusion, and Selpercatinib or Pralsetinib for positive RET gene fusion (8). However, adverse events are common in patients taking Lenvatinib and Sorafenib, including hypertension, fatigue, weight loss, diarrhea, and stomatitis. Remarkably, ^{18}F-FDG PET/CT can identify radioactive refractory disease, with SUVmax greater than 4.0 predicting the absence of ^{131}I avidity (10).

CONCLUSION

The reported case explores the use of immunological advancements in managing radioiodine refractory DTCs. While targeted therapies attenuate disease progression, they may not always provide overall survival benefits. Furthermore, the report emphasizes the importance of declaring DTCs as 'radioiodine refractory' for optimal initiation of immune therapy.

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