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Long-lasting Complete Remission Following Immunotherapy With Anti-PD1 Plus Anti-CTLA4 in a Polymetastatic Patient With NRAS (Q16R) Mutated Anaplastic Thyroid Carcinoma

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Abstract

Background/Aim: Anaplastic thyroid cancer (ATC) is a rare and aggressive malignancy. Its prognosis is poor, particularly in patients with distant metastasis. Treatment of ATC Is mostly palliative. In this report, we present the case of a patient affected by NRAS Q16R mutated, polymetastatic and multi-treated ATC, who showed complete remission of the disease after the use of an anti-PD1 and anti-CTLA4 doublet.

Case Report: We present the clinical case of an 82-year-old patient affected by polymetastatic anaplastic thyroid carcinoma carrying NRAS (Q16R) mutation, treated with surgery, radiotherapy and chemotherapy. Complete and long-lasting disease response was induced to the patient after immunotherapy anti PD1 plus anti CTLA4 (pembrolizumab + ipilimumab).

Conclusion: The combination of pembrolizumab plus ipilimumab may represent a therapeutic strategy in patients with NRAS (Q16R) mutated anaplastic thyroid cancer.

Keywords: Anaplastic thyroid cancer, target therapy, pembrolizumab, ipilimumab, molecular profiling, oligoprogressive, oligoresistance, PDL1, NRAS, molecular residual disease.

Introduction

Anaplastic thyroid carcinoma (ATC) is the most aggressive histological subtype of thyroid cancer and is one of the most frequent aggressive solid tumors with a disease-specific mortality rate close to 100% (1-2). ATC-related deaths are due to refractoriness to radioactive iodine (3-4).

Genomic profiling studies (5-9) have revealed that the essential molecular biomarkers for the diagnosis and prognosis of thyroid cancer are: BRAF mutation (10), RAS mutation (11), RET/PTC rearrangement (12), PAX8/PPARg rearrangement (13) and TERT promoter mutation (14). Moreover, tyrosine kinase inhibitors (15), thyroid hormone receptor inhibitors (16), radioactive iodine treatment (17), immunotherapy (18) and targeted gene therapy (19), allow a biological therapy pathway for this neoplasm.

Several studies of precision medicine have shown a better therapeutic index by using targeted therapies

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against specific molecular targets of different tumor types. These results have suggested the use of genetic-molecular classification instead of histological (20-29). While ATC patients with BRAF V600 mutation are eligible for anti-BRAF targeted therapy, combined or exclusive (7), there is no effective treatment for only NRAS mutated patients, hence the poor overall survival in this subgroup of patients.

This report presents the case of a patient affected by NRAS Q16R mutated, polymetastatic and multi-treated ATC who showed complete remission of the disease after the use of anti-PD1 and anti-CTLA4 doublet immunotherapy.

Case Report

In February 2021, a 77-year-old man underwent a left hip X-ray which documented the presence of a gross 13-cm lesion with evolutionary characteristics. Subsequent tests led to the diagnosis of thyroid cancer with a follicular histological type and anaplastic component (10%), associated with multiple bone metastases, almost ubiquitous at the level of the spine and pelvis, as well as in the laterocervical and mediastinal lymph nodes.

For this reason, in March 2021, the patient was subjected to a total thyroidectomy (pT2m N+ M1) and two-stage surgery of the bone secondary tumor affecting the left hemipelvis. Furthermore, between May and July 2021, due to the high risk of fracture at the level of the 3rd cervical vertebra and the 4th and 5th lumbar vertebra, he was subjected to fractionated stereotactic body radiation therapy (FSBRT) on the C3 lesion and L4-L5 vertebral stabilization,

In September 2021, radiometabolic therapy with RRA 200 mCi was started and FSBRT was performed on L5. On November 2021, the instrumental positron emission tomography (PET) re-evaluation documented lymph node, bone and thoracic progression disease (PD), with bilateral miliary dissemination of pathological micronodules in the lung parenchyma.

In February 2022, he contacted our center and showed previous examinations performed in a different center. The latest PET/CT scan showed progression of the disease after radiometabolic therapy with RRA 200 mCi; then systemic therapy was set up with paclitaxel 80mg/mq on days 1, 8 and 15 every 28 days + carboplatin AUC 2 on days 2, 9 and 16 every 28 days + pembrolizumab 200 mg every 21 days. In addition, extensive molecular profiling on thyroid tissue was requested. After the third cycle of systemic therapy, a PET documented stable disease (SD) according to RACIST criteria 1.1 version, while after the fifth cycle, complicated by hematological toxicity G2, the instrumental re-evaluation showed hepatic oligoprogression (single segment lesion of 2 cm) and oligoresistance of a supraclavicular lymph node. The remaining bone and lymph node secondaries had instead shown partial response (PR).

The liver lesion and the supraclavicular lymph node were then subjected to FSBRT. In April 2022, due to the toxicity of the previous line of chemotherapy, the patient started a second-line therapy with doxorubicin 75 mg/mq on days 1 and 2 every 3 weeks (first cycle was administered at 60 mg/mq) + pembrolizumab 200mg every 3 weeks, for a total of three cycles. In July 2022, as result of the SD after PET re-evaluation, an indication was given to continue maintenance therapy with pembrolizumab alone.

In December 2022, a TC/PET showed SD in all disease sites, except a significant increase in uptake in the known lesions of L4 and the left femur, both of which were subjected to FSBRT in January 2023. After radiotherapy on the sites of oligoprogression, the patient resumed therapy with pembrolizumab in January 2023.

The disease remained stable from January 2023 until September 2023, when PET showed mild progression in all disease sites, except for those irradiated and encountered local complete response (LCR). Based on the result of the molecular genetic test, the clinical picture, and the age of the patient, 2 cycles of systemic therapy with pembrolizumab plus ipilimumab were administered in October and November 2023. The third cycle was complicated by G3 gastrointestinal toxicity which required a 7-day hospitalization for dehydration secondary to profuse diarrhea and vomiting, not treated promptly due to the patient poor compliance. The toxicity was treated

with corticosteroid drugs, adequate hydration and with further specific therapy based on the results obtained from the study of the patient's intestinal microbiota.

Once the clinical picture was resolved with the administration of pembrolizumab plus ipilimumab, as well as with specific therapy for gastrointestinal toxicity, maintenance therapy was resumed with pembrolizumab every 28 days only.

Since January 2024, the latest PET/TC reassessments have highlighted complete response (CR) of the disease (Figure 1). The patient continues therapy with pembrolizumab without showing significant toxicities, except late hypophysitis, which appeared 16 weeks after the last doublet immunotherapy. This ACTH dependent-hypophysitis is currently on medical replacement therapy.

In addition to the imaging examinations, the disease was monitored at the molecular level using Signatera. The patient maintained a complete response to the ongoing therapy, as documented by the circulating tumor DNA (ctDNA) levels. The last evaluation on peripheral blood on 01/03/2025 confirmed the absence of ctDNA (Figure 2).

Signatera™ is a highly sensitive and personalized molecular test of residual disease (MRD) that uses circulating tumor DNA (ctDNA), designed specifically for each patient to help identify relapse earlier than standard diagnostic tools. It is designed to be used serially to detect relapses early, when it is undetectable with imaging, as well as assessing the effectiveness of treatment (as in this case) by quantitatively measuring ctDNA (30-37).

Discussion

It is now established that the expression of PD-L1 in solid tumors, including thyroid carcinoma, is predictor of improved outcomes in patients receiving PD-1/PD-L1-directed immunotherapy (38). In ATC, the expression of PD-L1 is induced during an active immune response; however, it may also be expressed during tumor escape. Thus, ATC patients are suitable candidates for anti-PD-1/PD-L1 (39, 40). The genes that control PD-L1 expression and its effects on cancer-related immune response are multiple (*e.g.*, NRAS) and the molecular mechanisms of interaction are complex and still poorly understood. Therefore, it is also essential to identify the interactions between PD-L1 and other molecular factors that can help guide the development of personalized treatment methods combined with immunotherapy and target therapy (41).

Until now, there is strong evidence on the use of immunotherapy in multimodal treatment, concomitant or sequential, in cancer patients whose neoplastic cells express BRAF, NTRK, ALK, RET, MSI, dMMR and TMB-H mutations. Instead, the efficacy of immunotherapy in patients with only NRAS mutated ATC is still uncertain (42).

Recent evidence has indicated that immunotherapy could be an effective treatment option for ATC. In a single-center study, the anti-PD-1 antibody pembrolizumab or nivolumab achieved an overall response rate (ORR) of 16% in 13 patients with advanced or metastatic ATC, including seven patients with BRAFV600 mutations (43). Similarly, in a phase 2 study of advanced/metastatic ATC (n=42), the experimental PD-1 antibody spartalizumab achieved an ORR of 19%, including three CRs and five PRs (44).

Regarding the use of anti-CTLA-4 antibody, the results of two studies (DREAMseq and SECOMBIT) demonstrated that nivolumab + ipilimumab followed by the BRAF inhibitor/MEK inhibitor doublet led to a superior overall survival in patients with advanced melanoma (although with BRAF mutation) compared to the opposite treatment sequence (45-46).

Abnormal activation of RAF-RAS-MAPK signaling is identified in over 30% of human tumors, including melanoma, hepatocarcinoma, lung carcinoma and T-cell lymphomas (47), and there is no effective targeted therapy for only NRAS-mutated solid tumors. Therefore, the treatment of solid tumors driven by only NRAS mutation represents a major clinical challenge.

Numerous studies have demonstrated the growing importance of circulating tumor DNA (ctDNA) in the clinical monitoring of solid tumors. This approach involves analyzing clonal somatic mutation (*e.g.*, Signatera), hotspot mutation, breakpoint junction or genomic amplification (30-37).

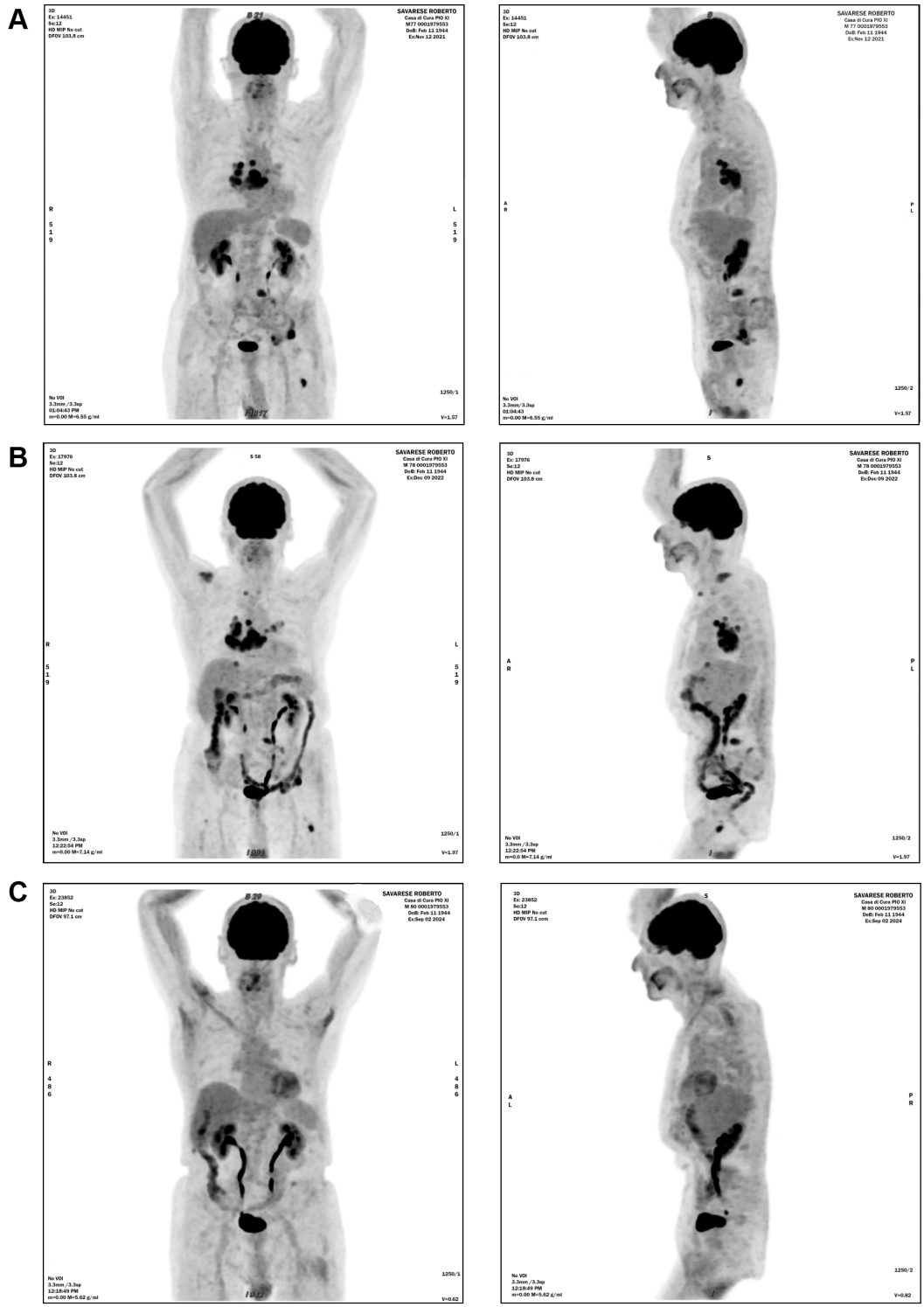

Figure 1. *Macroscopic disease response assessed with 18-fluoro-2-deoxyglucose positron emission tomography/computed tomography (PET/CT). (A) Restaging PET/CT before chemoimmunotherapy; (B) Oligoprogression treated whit radiation therapy; (C) Last evaluation (complete response).*

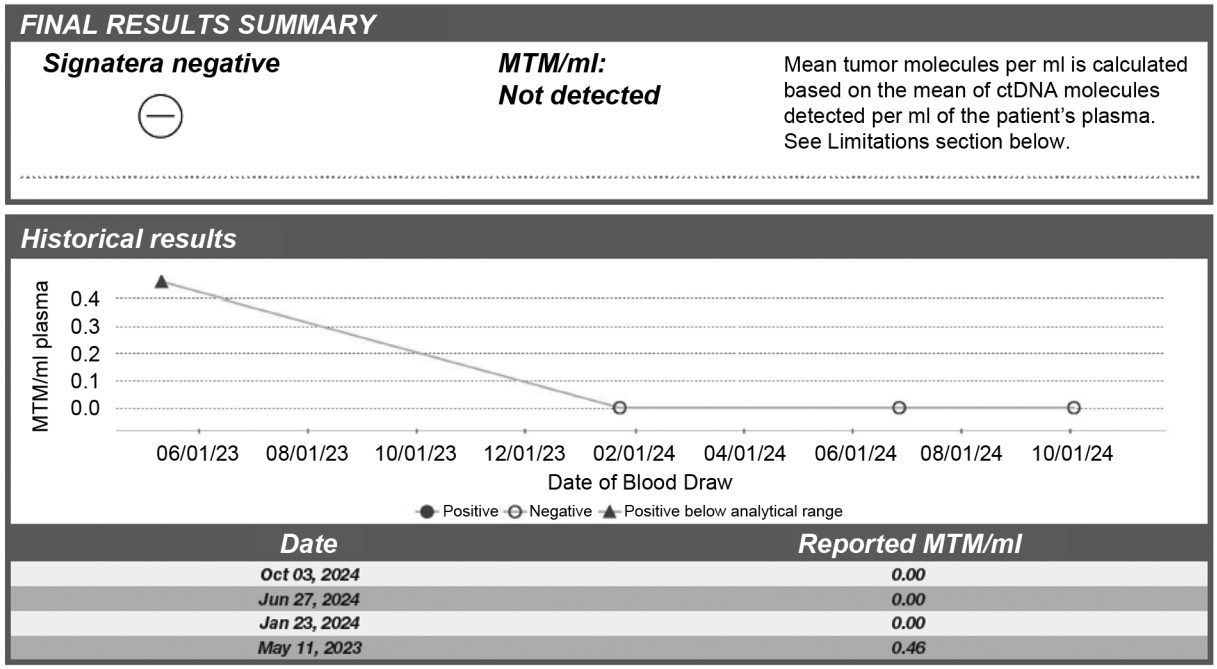

Figure 2. *Evolution of circulating DNA levels measured by Signatera.*

Currently, there are several reports of ongoing ATC studies involving PD-1/PD-L1 inhibitors (NCT05453799 and NCT05119296) or PD-1 combined with other treatments (NCT04171622, NCT04675710, NCT05696548, NCT04238624, NCT05659186, NCT03181100, NCT04400474, and NCT04579757) (48).

The dual anti-CTLA-4/PDL-1 combination is already used in patients with melanoma, kidney cancer, lung cancer and other solid tumors and predictive factors of response to this treatment are being researched (41). However, to the best of our knowledge, the only combination considered includes nivolumab as an anti-PDL1 drug and there are no studies investigating effectiveness and toxicities achievable with the use of pembrolizumab plus ipilimumab.

In the present report, although we present only one ATC case, we suggest that the addition of anti-CTLA4 may provide a greater probability of disease regression and an acceptable toxicity profile, compared to the anti-PD1 alone treatment, even when used simultaneously other anti-neoplastic treatment as radiotherapy, in patients affected by metastatic ATC. An advantage of anti-CTLA4 is that it has already been approved for the treatment of other solid tumors such as melanoma or kidney cancer.

Conclusion

In the present case, the long-lasting CR obtained after only 2 cycles of treatment with the dual anti-CTLA-4/PDL-1 combination, strengthens the hypothesis that immunotherapy may be effective in patients with only NRAS mutated ATC.

Conflicts of Interest

The Authors declare that there are no conflicts of interest in relation to this study.

Authors' Contributions

All Authors actively participated in the data collection. The article was written by Dimitri Anzellini and revised by Sergio Del Bianco.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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