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CASE REPORT

Complete Pathological Response and Severe Hypothyroidism under Pembrolizumab in Triple-Negative Breast Cancer: Between Triumph and Toxicity – A Case Report

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ABSTRACT

Pembrolizumab, a monoclonal anti–PD-1 immune checkpoint inhibitor, has become standard of care in early high-risk triple-negative breast cancer (TNBC) following the KEYNOTE-522 trial, which demonstrated significantly improved pathological complete response (pCR) and event-free survival. However, Pembrolizumab may induce immune-related adverse events (irAEs), particularly thyroid dysfunction, requiring careful monitoring and multidisciplinary management. We report the case of a 54-year-old postmenopausal woman diagnosed with stage T2N1M0 triple-negative breast cancer. She received neoadjuvant chemotherapy with Paclitaxel, Carboplatin, and Pembrolizumab according to the KEYNOTE-522 regimen. After the third cycle, she developed severe hypothyroidism (TSH 69.8 mIU/L, T4 2.7 pmol/L), which worsened during the fourth cycle (TSH 100 mIU/L). Treatment was temporarily postponed, and levothyroxine substitution was initiated after endocrinology consultation. Thyroid function improved within one week, allowing safe resumption of therapy. After completing six cycles, the patient underwent surgery, and pathological analysis revealed a complete pathological response (ypT0N0). She was referred for adjuvant radiotherapy. This case illustrates the dual nature of Pembrolizumab in TNBC: the capacity to induce deep tumor eradication and the risk of developing severe irAEs. Thyroid dysfunction is one of the most frequent endocrine complications of anti–PD-1 therapy. Early identification, rapid hormone replacement, and multidisciplinary coordination permitted treatment continuation and optimal oncologic outcome. In Algeria, where access to immunotherapy remains limited and costly, this case highlights the importance of systematic monitoring and pharmacovigilance. Pembrolizumab can achieve remarkable tumor responses in TNBC, yet requires vigilance for irAEs. Effective management of Pembrolizumab-induced hypothyroidism enabled uninterrupted treatment and a successful complete pathological response.

Keywords: Triple-negative breast cancer, pembrolizumab, immune-related adverse events, hypothyroidism, neoadjuvant therapy, pCR.

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CTNA : neoadjuvante chemotherapy
CTCAE : Common Terminology Criteria for Adverse Events
ER : Estrogen Receptor (récepteur aux œstrogènes)
EFS: Event-Free Survival (survie sans événements)
ESMO: European Society for Medical Oncology
FC: Free T4
HER2: Human Epidermal Growth Factor Receptor 2
ICIs : Immune Checkpoint Inhibitors (inhibiteurs de points de contrôle immunitaire)
irAEs: Immune-Related Adverse Events (événements indésirables immunitaires)
mIU/L : Milli-International Units per Liter (milli-unités internationales par litre)
MRI : Magnetic Resonance Imaging
NCCN: National Comprehensive Cancer Network
PD-1 : Programmed Death-1 (protéine de mort programmée 1)
PD-L1 : Programmed Death-Ligand 1
pCR : Pathological Complete Response (réponse pathologique complète)
PR : Progesterone Receptor (récepteur à la progestérone)
pmol/L : Picomoles per Liter (picomoles par litre
SBR : Scarff–Bloom–Richardson (grade histopronostique)
T4: Thyroxine (tétraiodothyronine)
TSH : Thyroid-Stimulating Hormone (hormone thyréostimulante)
TNBC : Triple-Negative Breast Cancer (cancer du sein triple négatif)
TDM TAP: Tomodensitométrie Thorax–Abdomen–Pelvis
Tis: Carcinoma in situ (stade histopathologique)
TA: Classification Sataloff – Tumeur (réponse tumorale)
NA: Classification Sataloff – Nœuds axillaires (réponse ganglionnaire)
ypT0N0 : Stade pathologique après traitement (post-thérapeutique)

1. INTRODUCTION

Triple-negative breast cancer (TNBC) accounts for 10–15% of breast cancers in Algeria **(1, 2)** and is associated with aggressive behavior and limited therapeutic options. Recent years have seen major advances with the introduction of immune checkpoint inhibitors (ICIs). Pembrolizumab is a humanized IgG4 monoclonal antibody targeting the programmed death-1 (PD-1) receptor, thereby inhibiting PD-1/PD-L1 interactions and restoring antitumor immunity. **(3)**

The pivotal KEYNOTE-522 phase III trial established pembrolizumab combined with neoadjuvant chemotherapy as a new standard for stage II–III TNBC. **(4)** The regimen led to a significant increase in pathological complete response (pCR), defined as the absence of residual invasive cancer in the breast and axillary lymph nodes (ypT0/Tis, ypN0). **(5)** Initial pCR rates reached approximately 65% with pembrolizumab versus 51% with chemotherapy alone. Long-term follow-up confirmed improvements in event-free survival and overall survival, validating the use of perioperative pembrolizumabin early high-risk TNBC. **(4)**

Despite its therapeutic efficacy, pembrolizumab can induce immune-related adverse events (irAEs) due to nonspecific immune activation. Endocrine irAEs are among the most frequent, especially hypothyroidism, which may occur in 10–15% of patients treated with anti-PD-1 agents. **(6)** The presentation ranges from transient thyroiditis to severe hypothyroidism requiring lifelong hormone replacement. These toxicities require close monitoring, particularly in middle-resource settings such as Algeria, where access to immunotherapy is growing but still limited by cost and availability. **(7, 8)**

This report describes a case of severe hypothyroidism occurring during neoadjuvant pembrolizumab therapy in a patient with TNBC in Algeria, emphasizing the importance of early detection, multidisciplinary management, and maintaining optimal oncologic outcomes.

2. CASE PRESENTATION

A 54-year-old postmenopausal woman with no significant comorbidities apart from a previous cholecystectomy presented with a self-detected right breast mass. She was managed at the Medical Oncology Department of Annaba for breast cancer. Her weight was 62 kg and height 154 cm, corresponding to a body mass index (BMI) of 26.1 kg/m², classified as overweight according to WHO criteria. Her family history was notable for ovarian cancer in her sister. Clinical examination revealed a palpable lesion in the upper outer quadrant of the right breast.

Core biopsy confirmed invasive carcinoma of no special type, grade 3 (SBR), with a triple-negative phenotype (ER-/PR-/HER2-). Staging classified the tumor as T2N1M0. The patient was planned for neoadjuvant treatment following the KEYNOTE-522 protocol, consisting of paclitaxel and carboplatinwith pembrolizumab, after ultrasound-guided clip placement. The pre-treatment workup revealed normal thyroid function tests. After three cycles, laboratory tests revealed marked hypothyroidism (TSH 69.8 mIU/L; T4 2.7 pmol/L), although the patient remained clinically stable. After a one-week delay, laboratory tests continued to worsen (TSH 100 mIU/L; T4 1.3 pmol/L). Chemotherapy was temporarily suspended. Endocrinologists recommended immediate initiation of levothyroxine 100 µg / day.

After one week, thyroid function began to normalize (TSH: 80 mIU/L; T4: 8 pmol/L), and treatment was safely resumed following a total 15-day delay. The patient completed six cycles, with the last administered on June 25, 2025. Surgery included a right tumorectomy with axillary lymph node dissection. Pathological examination revealed a complete pathological response (pCR) (ypT0N0, Sataloff TA, NA). The postoperative course was uneventful, and the patient was referred for adjuvant radiotherapy. The adverse event was reported to the national pharmacovigilance system. Ultimately, the patient had a favorable clinical outcome.

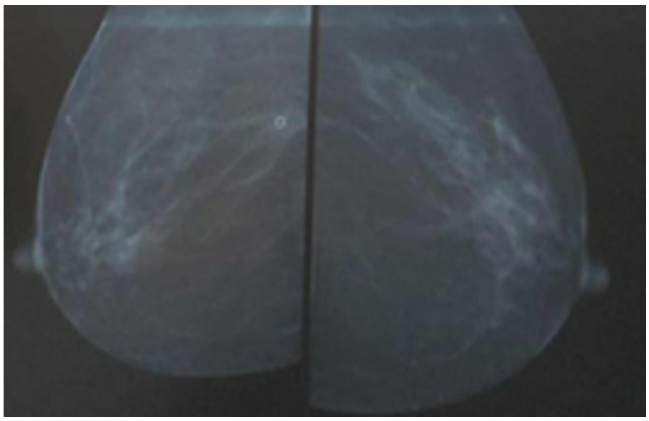

Figure 1. Mammography image.

3. DISCUSSION

Pembrolizumab has emerged as an essential component of neoadjuvant treatment in early triple-negative breast cancer (TNBC). The KEYNOTE-522 trial demonstrated that its addition to standard chemotherapy significantly improves pathological complete response (pCR) rates and overall survival, confirming the prognostic value of achieving pCR in reducing recurrence and improving long-term outcomes **(4)**

Despite these benefits, pembrolizumab is associated with immune-related adverse events (irAEs), particularly thyroid dysfunction, which represents one of the most frequent endocrine toxicities of immune checkpoint inhibitors (ICIs). The mechanisms underlying this dysfunction have been well described by Delivanis et al., who demonstrated that pembrolizumab-induced thyroiditis is driven by T-cell–mediated inflammation leading to destructive thyrotoxicosis, often evolving into permanent hypothyroidism. This pattern explains the frequent need for long-term levothyroxine supplementation. **(7)**. Although most cases remain mild to moderate, severe presentations have been reported. Mohammed et al. described a case of pembrolizumab-induced thyroid storm in a patient with TNBC, highlighting the potential for life-threatening endocrine complications. **(8)**

In contrast, our patient developed severe hypothyroidism with a TSH level >100 mIU/L; however, she remained minimally symptomatic clinically and required prompt therapeutic intervention. According to CTCAE criteria, this was classified as grade 2 hypothyroidism. This case highlights the wide variability in clinical presentation and underscores the importance of systematic thyroid function monitoring.

Current recommendations emphasize baseline and periodic assessment of TSH and free T4, ideally before each treatment cycle. In severe cases, temporary interruption of immunotherapy may be required while initiating appropriate endocrine management. Early endocrinology referral and timely initiation of levothyroxine therapy are essential to stabilize thyroid function. In our case, prompt recognition and management allowed the continuation of pembrolizumab without compromising therapeutic efficacy, ultimately resulting in a complete pathological response (pCR). **(9)**

In addition, recent literature provides further guidance regarding the optimal management of endocrine irAEs. Stelmachowska-Banas **(9)** emphasizes that ICI-induced thyroid dysfunction typically follows a biphasic pattern of destructive thyroiditis leading to permanent hypothyroidism, and they highlight the importance of early identification through routine TSH and free T4 monitoring every 4 to 6 weeks. Their review reiterates that levothyroxine replacement remains the cornerstone of treatment for overt hypothyroidism, with dosage adjusted according to age, comorbidities, and severity of hormone deficiency.

Similarly, the Endotext clinical guidelines updated by Elshimy et al. **(10)** provide detailed recommendations regarding dosing strategies. They advise initiating levothyroxine at full replacement doses (approximately 1.6 µg/kg/day) in younger patients without cardiovascular disease, while starting at lower doses (25–50 µg/day) in older adults or those with cardiac comorbidities. The authors also underscore the need to rule out adrenal insufficiency before starting thyroid hormone therapy, as unrecognized cortisol deficiency could precipitate adrenal crisis. According to these guidelines, thyroid hormone replacement can generally be continued in parallel with immunotherapy, except in severe or unstable cases. **(9, 10)**

The inclusion of these contemporary recommendations reinforces the approach applied in our case, where early detection, endocrinology involvement, and timely initiation of levothyroxineenabled the safe continuation of pembrolizumab. This favorable outcome is consistent with observations suggesting a potential association between endocrine irAEs and improved oncologic response, although this relationship remains under investigation.

In Algeria, despite the availability of pembrolizumab since 2018, access remains limited due to cost constraints. This highlights the importance of developing optimized and cost-effective management strategies. Our case reinforces the need for multidisciplinary expertise, standardized monitoring protocols, and strengthened pharmacovigilance to ensure safe and effective integration of immunotherapy within national oncology practice.

4. CONCLUSION

Pembrolizumab-based neoadjuvant therapy can induce profound tumor responses in TNBC, as evidenced by the complete pathological response in this patient. Nevertheless, clinicians must remain vigilant for immune-related toxicities such as severe hypothyroidism, which may require temporary treatment interruption and hormone replacement. Early recognition and coordinated multidisciplinary management allowed safe continuation of therapy and an excellent oncologic outcome. In Algeria, strengthening monitoring protocols and pharmacovigilance is essential to optimize the use of immunotherapy.

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