East African Scholars Journal of Medicine and Surgery
Abbreviated Key Title: EAS J Med Surg
ISSN: 2663-1857 (Print) & ISSN: 2663-7332 (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-7 | Issue-5 | May-2025 | DOI: https://doi.org/10.36349/easjms.2025.v07i05.006

Case Report

Double HER2 Blockade and Iatrogenic Hypothyroidism During Treatment of HER2-Positive Metastatic Breast Cancer: A Clinical Case and Literature Review

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Article History
Received: 27.03.2025
Accepted: 03.05.2025
Published: 19.05.2025

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: HER2-positive metastatic breast cancer represents a significant therapeutic challenge. Its prognosis has been altered thanks to significant advances in targeted anti-HER2 therapies. These treatments, such as trastuzumab and pertuzumab, have significantly improved the management of this pathology, enhancing patient survival, but are also responsible for adverse effects. Hypothyroidism, although less frequent than other complications, is an important side effect to recognize and manage. This clinical case presents a 47-year-old patient with HER2-positive metastatic breast cancer treated with chemotherapy combined with a dual anti-HER2 blockade using trastuzumab and pertuzumab, along with letrozole. After 52 cycles of dual blockade, the patient developed overt hypothyroidism. Levothyroxine replacement therapy improved her symptoms. This case illustrates the clinical importance of endocrine monitoring in patients receiving targeted anti-HER2 therapies, highlighting the need for a multidisciplinary approach to optimize the management of adverse effects and the quality of life of patients. A diagnostic delay of hypothyroidism can potentially impact the prognosis of the disease.

Keywords: Metastatic breast cancer, double HER2 blockade, Iatrogenic Hypothyroidism.

INTRODUCTION

Breast cancer is a heterogeneous disease, classified into several molecular subtypes based on the expression of hormone receptors and the human epidermal growth factor receptor 2 (HER2). The HER2-positive subtype represents approximately 15 to 20% of breast cancers [1]. It is characterized by amplification of the HER2 gene, leading to excessive production of the HER2 protein on the surface of tumor cells. This protein is a receptor that plays a crucial role in tumor cell proliferation and survival. Anti-HER2 therapies have revolutionized the management of HER2-positive breast cancer. They aim to specifically block the activity of the HER2 protein, thereby inhibiting tumor growth and proliferation. Among these therapies, trastuzumab and pertuzumab are two widely used monoclonal antibodies, often in combination [2].

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of the HER2 protein, preventing the activation of its receptor and the initiation of the intracellular signaling cascade. It is administered intravenously (IV) or subcutaneously (SC) and is a standard treatment for HER2-positive breast cancers, whether localized or metastatic [3]. Pertuzumab is also a humanized monoclonal antibody that binds to a different domain of the HER2 protein than trastuzumab, thus blocking another signaling pathway. Pertuzumab is administered IV and more recently SC [4]. When used in combination, these two antibodies act synergistically to block the HER2 signaling pathway and induce a more effective antitumor response [5]. The combination of these two drugs has therefore become the standard treatment for HER2-positive breast cancers. However, despite their efficacy, it is important to consider the potential adverse effects of these treatments, such as endocrine disorders, which are often underdiagnosed and require specific monitoring and management.

CLINICAL CASE

A 47-year-old female patient, followed since 2016 for breast cancer initially diagnosed at stage T2N1M0. Her therapeutic journey began with

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neoadjuvant chemotherapy consisting of three cycles of FEC100 (5-fluorouracil, epirubicin, cyclophosphamide) every three weeks, followed by three cycles of docetaxel administered at the same frequency. A complete clinical response, characterized by the disappearance of the tumor nodule, was then observed. The patient was lost to follow-up until 2020, when a local recurrence appeared in the form of a large nodule, infected, oozing, and associated with inflammatory signs and an orange peel appearance.

Her management at the gynecology department revealed, by thoraco-abdomino-pelvic computed tomography (CT-TAP), a large left breast mass associated with pulmonary metastases. A mastectomy was then performed. The anatomopathological examination of the surgical specimen confirmed an infiltrating carcinoma of the not otherwise specified (NOS) type, measuring 15 x 14 x 5 cm, with cutaneous invasion. The tumor was classified as T4b N1 M1. Immunohistochemical analysis revealed a strong expression of estrogen receptors (ER) at 80%, an absence of progesterone receptor (PR) expression, and an overexpression of HER2 (3+). The CA 15-3 level was elevated at 118 UI/mL. Cardiac, hepatic, and renal assessments were unremarkable, and the patient had no history of thyroid disease.

First-line treatment with docetaxel, trastuzumab, and pertuzumab, administered every three weeks, was initiated. After six cycles of this polychemotherapy, a CT-TAP scan showed a complete radiological response, associated with a normalization of the CA 15-3 level (12.82 UI/mL). A multidisciplinary team meeting (MTM) decided to implement maintenance therapy with dual anti-HER2 blockade (trastuzumab and pertuzumab) combined with letrozole 2.5 mg. Trastuzumab was initially administered intravenously for 30 cycles before transitioning to subcutaneous administration.

After 52 cycles of dual anti-HER2 blockade, the patient complained of unusual fatigue, associated with a weight gain of 3 kg and the progressive onset of lower limb edema (Figure 1). The cervical examination was normal (Figure 2). The ultrasensitive TSH measurement revealed a value of 25.35 mUI/L (reference values: 0.4 to 4.5 mUI/L), associated with a collapse of T3 and T4 levels. Anti-TPO and anti-TG antibodies were negative. Cervical ultrasound showed no thyroid abnormalities. An endocrinological consultation concluded an iatrogenic hypothyroidism.

At the multi-disciplinary team meeting, it was decided to initiate hormone replacement therapy with levothyroxine at an initial dose of 75 µg while continuing treatment with trastuzumab, pertuzumab, and letrozole. The clinical and biological evolution under this new treatment was favorable.

Figure 1: The patient with lower limb edema

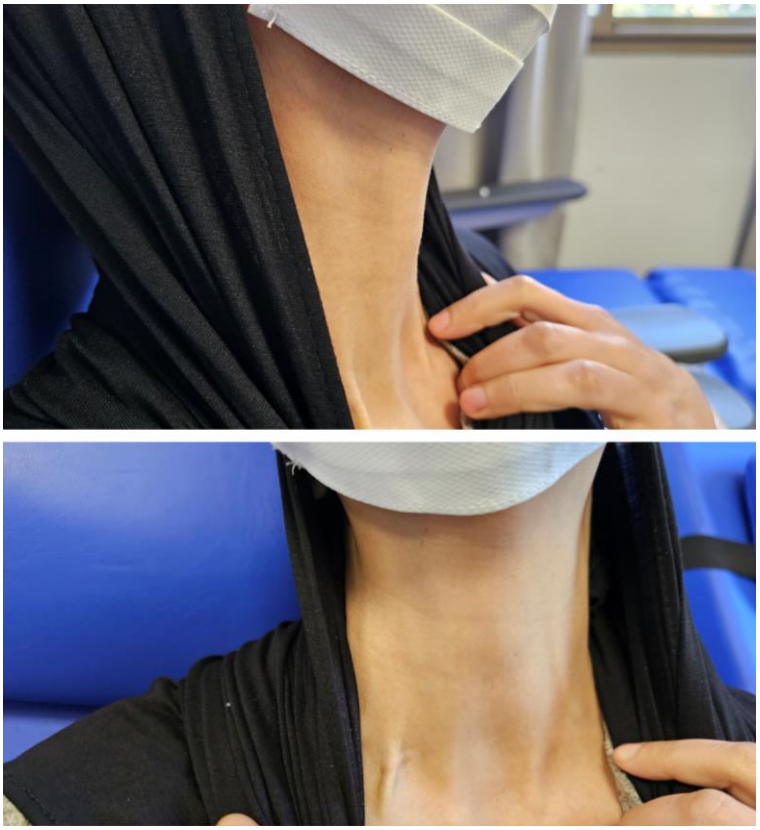

Figure 2: Cervical examination without abnormalities

DISCUSSION

This clinical case presents a patient with HER2-positive metastatic breast cancer who initially responded remarkably to the docetaxel-dual blockade combination. The complete response obtained and subsequently maintained with dual anti-HER2 blockade combined with letrozole demonstrates the efficacy of these targeted therapies. The onset of hypothyroidism after 52 cycles of treatment, however, underscores the challenges of long-term management, as prolonged treatments can cause endocrine disorders. Iatrogenic hypothyroidism induced by anti-HER2 therapies is a rare phenomenon. A randomized study including 3386 breast cancer patients showed that 1678 received intravenous trastuzumab, an average of 18 times for 51 weeks. Only 0.3%, or 4 patients, developed thyroid disease. The literature reports 3 other cases of this complication: 1 after intravenous injection [6] and 2 after subcutaneous injection [7].

Although the exact mechanisms are not yet fully elucidated, it is suggested that these treatments may interfere with thyroid function by disrupting the synthesis and conversion of thyroid hormones or by inducing local inflammation [8, 9]. The fact that anti-TPO and anti-TG antibodies are negative in this case suggests a non-autoimmune origin and supports the hypothesis of a direct effect of the treatment on thyroid function. The absence of visible thyroid abnormalities on cervical ultrasound also reinforces this hypothesis. Hypothyroidism may be related to the direct toxicity of monoclonal antibodies; this type of side effect has also been reported with anti-HER2 tyrosine kinase inhibitors [10].

Another hypothesis involves recombinant human hyaluronidase (rHuPH20), an essential component of subcutaneous formulations. This enzyme degrades hyaluronic acid to facilitate the release and absorption of subcutaneous drugs. An increase in hyaluronic acid is observed in inflamed thyroid tissues [11], and it is suggested that the degradation of this substance by rHuPH20 could promote the accumulation of T lymphocytes in the thyroid, as observed in research models on colorectal cancer [12]. Thus, there may be an association between subcutaneously administered trastuzumab and autoimmune thyroid diseases in patients with HER2-positive breast cancer, due to an increased recruitment of T lymphocytes induced by rHuPH20 [7].

The clinical presentation, with unusual fatigue and weight gain, is not specific to hypothyroidism; these symptoms can sometimes be mistakenly attributed to the neoplastic disease. Monitoring thyroid function during the use of anti-HER2 treatments is therefore essential. This case highlights the need for regular screening and follow-up of thyroid function by measuring TSH levels before the initiation of treatment, followed by regular monitoring during treatment and follow-up, using a multidisciplinary approach including oncologists and endocrinologists.

CONCLUSION

This observation underscores the importance of close monitoring of thyroid function in patients treated with anti-HER2 therapies, due to the risk of endocrine side effects. A multidisciplinary approach, including oncologists and endocrinologists, is essential to screen for and optimize the management of adverse effects of anticancer treatment and improve the quality of life of patients.

Conflicts of Interest: The authors of this article declare that they have no conflicts of interest. The authors are solely responsible for the information and writing of this article.

Funding: The authors of this article have received no grants or funding for this study from any institutions or educational bodies.

Consent: Informed consent was obtained from the patient for this publication and the use of images in this publication.

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Cite This Article: Touimri Youssef, Taleb Imad, Tadlaoui Abderrahman, Toreis Mehdi, Bazine Aziz, Fetouhi Mohammed (2025). Double HER2 Blockade and Iatrogenic Hypothyroidism During Treatment of HER2-Positive Metastatic Breast Cancer: A Clinical Case and Literature Review. *East African Scholars J Med Surg, 7*(5), 86-89.