

Autoimmune hypothyroidism and trastuzumab therapy: a rare association

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Summary

We report a case of a woman with a diagnosis of breast cancer who unintentionally started gaining weight, feeling tired, and constipated 44 weeks after the initiation of trastuzumab. Hypothyroidism secondary to an autoimmune thyroiditis associated with trastuzumab was diagnosed, the first case described in Portugal and the fourth case described worldwide. Our intention regarding the publication of this case report is to alert the clinicians treating people with trastuzumab that they should ask the patients about symptoms of hypothyroidism and should screen the thyroid function of the patients before, during, and after the initiation of trastuzumab.

Learning points

- Trastuzumab is a humanized MAB used in HER2-positive breast and gastric cancer.
- Trastuzumab-associated autoimmune thyroid disease (AITD) is rare (incidence rate in an RCT of 0.3%).
- Manifestations of autoimmune thyroiditis associated with trastuzumab resemble those of hypothyroidism in other clinical contexts, but the presence of goiter is highlighted as a reason for medical evaluation. Biochemically, it is characterized by an increased thyroid-stimulating hormone (TSH) with or without a low FT4/FT3, and sonographically with a pattern of thyroiditis.
- The treatment consists of levothyroxine, in a dose of 1.6–1.8 µg/kg/day, with re-evaluation of the thyroid function in 4–6 weeks.
- We report the first case of autoimmune thyroiditis secondary to trastuzumab in Portugal.
- It is important to evaluate the thyroid function before, during, and after the initiation of this therapeutic agent.

Background

Trastuzumab is a humanized MAB directed against human EGF receptor 2 (HER2) and is used mainly in the treatment of HER2-positive breast cancer and HER2-positive gastric cancer(1). Although it is generally well tolerated, a small proportion of patients develop adverse reactions, namely autoimmune thyroid disease (AITD).

In a randomized clinical trial (RCT) that enrolled 3386 patients with breast cancer, 1678 received a median of 18 i.v. infusions of trastuzumab, during a median

treatment duration of 51 weeks, the incidence rate of AITD was 0.3% (four cases). To date, only three cases of trastuzumab-associated AITD have been described and are available in the literature: one case by Min *et al.* (2) and two cases by Sánchez-Bayona *et al.* (3). The case reported by Min *et al.*, like the three cases that occurred in the RCT mentioned above, was detected after an i.v. infusion of trastuzumab, but the two cases described by Sánchez-Bayona *et al.*, were detected after s.c. administration of the drug.



The underlying mechanism is still unknown and probably differs between the types of formulation. In the case of i.v. infusion, Weetman (4) suggested the role of immune reconstitution syndrome in the pathogenesis of AITD and in the case of s.c. administration, Rosengren *et al.* (5) and Alaniz *et al.* (6) suggested that the recruitment of T-cells induced by the recombinant human hyaluronidase (a component of the s.c. formulation of trastuzumab), which degrade the hyaluronan present in the extracellular matrix of the thyroid gland, can be an explanation.

Case presentation

We report a case of a 47-year-old woman, without known prior thyroid or autoimmune disease and without a history of the same in the family, with a diagnosis of breast cancer in the right breast 1 year ago, in March 2021, at an initial stage cT2N1M0 (one right axillary lymphadenopathy).

A biopsy of the breast lesion revealed a grade II invasive carcinoma of no special type, with positivity for estrogen receptor and human EGF receptor 2 (HER2), and with a Ki67 index of 20%. She was promptly started on neo-adjuvant chemotherapy (NACT): initially, for 4 weeks, with doxorubicin and cyclophosphamide (ACx4), and later, during the next 12 weeks, with weekly paclitaxel. Simultaneously, she was treated with a targeted therapy towards HER2, namely trastuzumab and pertuzumab. Then, 1 month later in September 2021, she underwent a sentinel lymph node biopsy, with a negative result, and a breast-conserving surgery (lumpectomy). After the surgery, the right breast and the homolateral lymphatic drainage areas were irradiated with 50 gray (Gy) for 40 days, with a subsequent boost in the tumoral bed with a dose of 10 Gy for 7 days, which was concluded in January 2022.

Investigation

After completing neo-adjuvant chemotherapy (NACT), lumpectomy, and adjuvant radiotherapy with good tolerance, she remained medically treated with trastuzumab (420 mg once every 2 weeks, i.v. administration), goserelin (3.6 mg once a month, s.c. administration), tamoxifen (20 mg once daily, oral administration), and zoledronic acid (4 mg once a year, i.v. administration).

In the mid of January, approximately 44 weeks after the first administration of trastuzumab, she started unintentionally gaining weight (4 kgs in approximately 1 month), became tired easily, and she complained of constipation also. The onset of hypertension, previously unknown in the patient's past history, was also noteworthy.

Her general medical practitioner requested a thyroid function test in February, which, at that time, revealed a thyroid-stimulating hormone (TSH) of 188 μ UI/L (reference value (RV): 0.27–4.20 μ UI/L) and a free thyroxine (FT4) of 2.4 pmol/L (RV: 12–22 pmol/L) although she did not start therapy at that time.

She also underwent a thyroid ultrasonography, which revealed an increased thyroid gland (right lobe with 56 × 21 × 22 mm and left lobe with 62 × 22 × 26 mm), with a heterogeneous hypoechoic parenchyma, without identifiable nodules, highly suggestive of thyroiditis.

She was then referenced to our Endocrinology department without initiation of any treatment. We evaluated her in March 2022: she appeared tired, with a euthymic tumour and a pale and dry skin and without oedema or macroglossia. Cervical region examination revealed a non-pulsatile and diffusely enlarged thyroid gland without nodules or lymphadenopathies (Fig. 1). Her blood pressure was 156/99 mmHg, and her heart rate was 81/min.

Thyroid function test results were promptly collected, revealing thyroid-stimulating hormone (TSH) level of 180.6 μ UI/mL (RV: 0.27–4.20 μ UI/L), a FT4 of 0.49 ng/dL (RV: 0.89–1.76 ng/dL), a free triiodothyronine (FT3) of 1.99 pg/mL (RV: 2.30–4.20 pg/mL), and antibodies against thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO) of 47.39 UI/mL (RV: < 4.5 UI/mL) and 35.70 UI/mL (RV: < 60 UI/mL), respectively.

Her blood cortisol level in the morning (at 11:00 am) was 11.03 μ g/dL (RV: 4.3–22.4 μ g/dL).

Treatment

The patient was immediately started on supplementation with 75 μ g/day of levothyroxine (LT4). Simultaneously, because we did not have the morning serum cortisol value immediately available, albeit the risk of adrenal crisis was low, we decided to initiate 5 mg of prednisolone. One week



Figure 1

Anterior and lateral inspection of the cervical region on the first visit. A small, non-pulsatile goiter was observed, which motivated the initial study.



Table 1 Laboratory assessment of the patient. Evolution of analytical parameters throughout the course of the disease after the start of levothyroxine.

	Baseline	Treatment start	Follow-up			Normal range
	20/02/2022	24/03/2022	20/04/2022*	19/08/2022†	14/12/2022‡	
TSH (μUI/mL)	188	180.6	8.6	0.3	1.4	0.55–4.20
T4L (ng/dL)	0.18	0.49	1.27	1.37	1.13	0.89–1.76
T3L (pg/mL)	–	1.99	2.92	–	–	2.30–4.20
Anti-Tg (UI/mL)	–	47.39	–	–	–	<4.5
Anti-TPO (UI/mL)	–	35.70	–	–	–	<60
Cortisol (μg/dL)	–	11.03	–	–	–	–
Treatment						
LT4 (μg/day)	–	75	100	88	88	–

*4 weeks later; †20 weeks later; ‡36 weeks later.

later, the patient reported a clear clinical improvement, feeling less tired, and her bowel function became normalized.

Her thyroid function after 1 week, revealed a normalization of the free fractions of the thyroid hormones, with a FT4 of 0.96 ng/dL (RV: 0.89–1.76 ng/dL) and a FT3 of 2.76 pg/mL (RV: 2.30–4.20 pg/mL). We maintained the dose of LT4 and gradually reduced the dose of glucocorticoid till its total suspension.

Outcome and follow-up

Four weeks after the initiation of LT4, the thyroid-stimulating hormone (TSH) was near a normal value (8.6 μUI/mL), again with the free fractions of the thyroid hormones in the normal range (Table 1). The thyroid ultrasonography that day revealed an increased thyroid gland, with lobulated contours, with the left lobe more prominent than the right and with a heterogeneous hypoechoic parenchyma, with multiple pseudonodular areas but without identifiable nodules. The intraglandular vascularity was diffusely increased (Fig. 2). The dose of LT4 was increased to 100 μg/day and, after four months, the TSH was 0.3 μUI/mL, slightly below the reference range. At that time, the patient was completely asymptomatic, without goiter and with a normotensive blood pressure profile. The dose of LT4 was then switched to 88 μg/day, and four months later, her thyroid function normalized (FT4: 1.13 ng/dL and TSH: 1.4 μUI/mL).

Discussion

Although the incidence of trastuzumab-associated AITD is very rare, it is important to alert the clinicians for its possibility because not only trastuzumab is used in a

substantial amount of patients for different circumstances (not only for breast cancer) but also because AITD, if not promptly diagnosed and treated, can have a severe impact on patients' quality of life.

Moreover, the symptoms of hypothyroidism, namely fatigue, can easily be overlooked as a result of the neoplasm, further delaying the diagnosis (and consequently the treatment) of AITD.

The case that we report shows the importance of recognizing this entity, because, although our patient was promptly diagnosed with hypothyroidism, with a frankly elevated thyroid-stimulating hormone (TSH) value, her general medical practitioner had not initiated

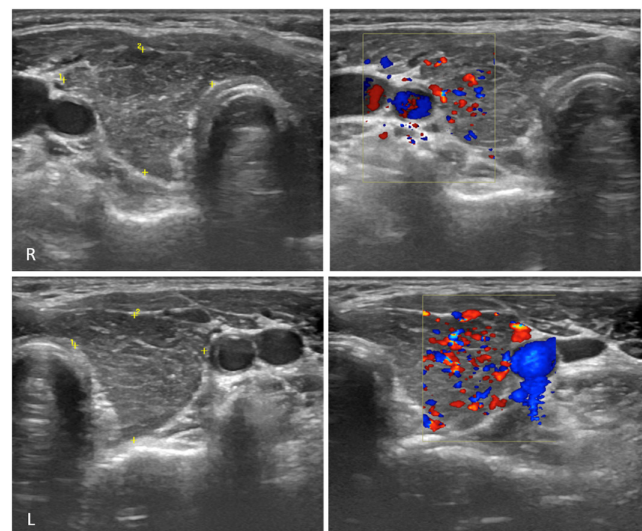


Figure 2

Thyroid ultrasonography revealing an enlarged thyroid gland – right lobe (superior left image) (24 × 21 × 58 mm) and left lobe (inferior left image) (21 × 21 × 65 mm), with lobulated contours and a heterogeneous hypoechoic parenchyma with multiple pseudonodular areas. The intraglandular vascularity was diffusely increased.



any treatment, having maintained the poor quality of life of the patient for approximately one month and a half, fortunately without more negative consequences. This undervaluing of analytical alterations, in part, may have been due to a good general condition that the patient presented and the absence of relevant comorbidities.

Comparing with the only three cases available in the literature, the case that we report is very similar to the two cases described by Sánchez-Bayona *et al.* (3). Our patient developed symptoms of hypothyroidism, confirmed biochemically with a strongly increased TSH, approximately 44 weeks after the onset of trastuzumab, and their patients 12 and 24 weeks after. On the other hand, the case described by Min *et al.* (2) did not report any symptoms of hypothyroidism; instead, the case presented as a voluminous goiter and remained always, biochemically, in euthyroidism.

The existence of a pre-existing autoimmune disease seems to predispose to trastuzumab-associated AITD, but like the case described by Min *et al.* (2) and one of the cases of Sánchez-Bayona *et al.* (3), our patient did not present any previous known autoimmune disease of the thyroid gland or any other organ and presented normal thyroid function tests in 2016.

So, in conclusion, this is the first case of autoimmune thyroiditis associated with trastuzumab reported in Portugal and is part of the few cases reported worldwide of thyroid dysfunction associated with this drug.

The case highlights the importance of having the knowledge about this association, and while making the diagnosis, it is of utmost importance to evaluate the thyroid function before, during, and after the initiation of this therapeutic agent. In this line of thought, the screening of antithyroid antibodies, namely anti-TPO and anti-Tg, should also be done before the initiation of trastuzumab to identify patients at a higher risk of developing hypothyroidism and to necessitate, therefore, a closer follow-up.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent for publication of the clinical details and clinical images was obtained from the patient.

Author contribution statement

The main author did the research and wrote the entire article. The second co-author did the revision of the entire article. The third co-author is the physician of the patient and obtained the informed consent and did the ultrasonography of the thyroid gland and the revision of the entire article.

References

- 1 Oh DY & Bang YJ. HER2-targeted therapies – a role beyond breast cancer. *Nature Reviews. Clinical Oncology* 2020 **17** 33–48. (<https://doi.org/10.1038/s41571-019-0268-3>)
- 2 Min HK, Kim IH, Kim JY, Ban TH, Kim KH, Ha J & Kim JH. Trastuzumab-associated autoimmune thyroid disease in a patient with metastatic breast cancer. *Korean Journal of Internal Medicine* 2016 **31** 608–611. (<https://doi.org/10.3904/kjim.2014.031>)
- 3 Sánchez-Bayona R, Garcia del Barrio MA, Alegre E, Fernandez-Hidalgo OA & Eslava MS. Trastuzumab and thyroid dysfunction: an association to be aware of. *Journal of Cancer Research and Therapeutics* 2022 **18** 1183–1185. (https://doi.org/10.4103/jcrt.JCRT_66_19)
- 4 Weetman A. Immune reconstitution syndrome and the thyroid. *Best Practice and Research. Clinical Endocrinology and Metabolism* 2009 **23** 693–702. (<https://doi.org/10.1016/j.beem.2009.07.003>)
- 5 Rosengren S, Dychter SS, Printz MA, Huang L, Schiff RI, Schwarz HP, McVey JK, Drake FH, Maneval DC, Kennard DA *et al.* Clinical immunogenicity of rHuPH20, a hyaluronidase enabling subcutaneous drug administration. *AAPS Journal* 2015 **17** 1144–1156. (<https://doi.org/10.1208/s12248-015-9782-0>)
- 6 Alaniz L, Rizzo M, Malvicini M, Jaunarena J, Avella D, Atorrasagasti C, Aquino JB, Garcia M, Matar P, Silva M *et al.* Low molecular weight hyaluronan inhibits colorectal carcinoma growth by decreasing tumor cell proliferation and stimulating immune response. *Cancer Letters* 2009 **278** 9–16. (<https://doi.org/10.1016/j.canlet.2008.12.029>)

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