

*Case report*

## Breast Cancer and Graves' Disease

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### SUMMARY

**Introduction.** Numerous clinical trials have proven the connection between two glandular organs, in this case, the breast and the thyroid gland. The occurrence of breast cancer (BC) is increased in patients with autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease). Patients with Graves' disease have a significantly smaller number of described cases of BC than those with diagnosed Hashimoto's thyroiditis.

**Case report.** A 57-year-old female patient came to the emergency center with difficulty breathing. During the examination, ophthalmopathy, weakened breath sound and mastitis of both breasts were found. Hormonal analysis showed the following values: TSH 0.00 (0.3 - 5.5 mIU/L), FT4 32.90 (11.5 - 23 pmol/L), TSHRA<sub>t</sub> 19 (0.0 - 1.1 U/L), TPOA<sub>t</sub> 234 (0.0 - 12 IU/ml), TgA<sub>t</sub> > 2000 (0.0 - 30.0 IU/ml). A diagnosis of Graves' disease was established and therapy with thyrosuppressant was started immediately. A multi-detector computed tomography (MDCT) showed a left breast tumor with metastases in the supraclavicular and axillary lymph nodes, infiltration of the tumor into the skin and subcutaneous tissue, as well as metastases in the bones. A biopsy of the breast tumor was performed, and PH findings indicated poorly differentiated ductal carcinoma of the breast, HER-2+ group of tumors.

**Conclusion.** The early detection of thyroid disease would not lead to the development of a malignant process, and that is why doctors in their clinical work must recognize the first signs of thyroid disease in their patients, and immediately start with therapy to reduce the potential risk of BC. There is a significant role in using screening tests to discover breast cancer in patients with untreated or inadequately treated hypo- and hyperthyroidism.

**Keywords:** breast cancer, Graves' disease, autoimmune thyroid disorders

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## INTRODUCTION

Breast cancer (BC) is the most common cancer in women with an incidence of 0.5% growth per year, with 576,300 affected women in Europe in 2020 (1). Numerous clinical trials have proven the connection between two glandular organs, in this case, the breast and the thyroid gland. Beatson first described in 1896 the association between thyroid disease (TD) and BC (2 - 5). One of the potential mechanisms of breast cancer development is related to the mechanism of thyrotropin (TSH) and thyroid hormones (TH) action, which achieve their effect through the proliferation of breast cells, influence on angiogenesis, and the occurrence of dysplastic changes (6 - 8). The occurrence of breast cancer is increased in patients with autoimmune thyroid disease (Hashimoto's thyroiditis and Graves' disease). Still, it is not proven to increase the risk in patients with non-immune thyroid disease. In patients with Graves' disease, there is a significantly smaller number of described cases of BC than in those with diagnosed Hashimoto's thyroiditis (9, 10). In the blood of these patients, autoantibodies such as thyroglobulin antibody (TGA), thyroid microsomal antibody (TPOAb), and thyroid-stimulating receptor antibody (TRAb) can be detected. Previous studies have shown that patients with high TPOAb had a lower risk of BC and lymph node metastases than those with positive TRAb (11, 12). The expression of the TSH receptor is increased in breast cancer tissues. The binding of TRAb for TSH-R induces cyclic adenosine monophosphate (cAMP) formation and mitogen-activated protein kinase (MAPK) activation and this process results in malignant cell proliferation (13 - 15). The study in Sweden with

18,156 patients with Graves' disease found a higher risk of breast cancer (16).

In this brief communication, we report a female patient with untreated Graves' disease which was complicated by a severe ophthalmopathy and with the acute-onset development of bilateral ductal breast carcinoma and bone metastases.

## CASE REPORT

A 57-year-old female patient came to the emergency center with severe breathing. During the examination, ophthalmopathy, weakened breath sound and mastitis of both breasts were found. An X-ray of the lungs was performed, where a unilateral effusion was described on the left. A pleural puncture was performed for diagnostic and therapeutic purposes, whereby 2000 ml of serohemorrhagic content was evacuated. Pleural fluid was sent for microbiological and pathological examination. After those initial examinations and diagnostic procedures, the patient was hospitalized for further diagnostics and therapy. In history, the patient reported weakness, malaise, suffocation, and a loss of 10 kg in a month. She said that the changes in the eyes and breasts occurred 15 days before reporting to the doctor. Significant exophthalmos presented with the signs of conjunctivitis (Figure 1), goiter of the thyroid gland, erythematous, painless breasts, indented nipples (Figure 2), enlarged axillary lymph nodes, right 2 x 2 cm, left 2 x 1.5 cm. She denied allergies and previous illnesses and surgeries and she was not taking any chronic therapy. Family history revealed diabetes mellitus and hypertension. Complete blood tests and biochemical tests were performed, the findings were within the reference ranges, except for

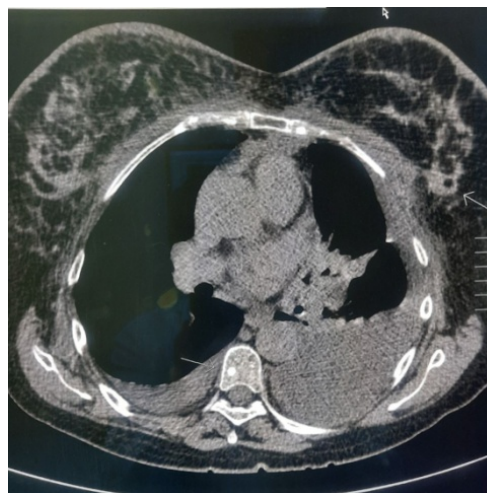


**Figure 1:** Exophthalmos before therapy



**Figure 2:** Mastitis carcinomatosa before therapy

the elevated tumor marker CA 15.3 56.6 (0 - 30 U/ml). Hormonal analysis showed the following values: TSH 0.00 (0.3 - 5.5 mIU/L), FT4 32.90 (11.5 - 23 pmol/L), TSHRA<sub>t</sub> 19 (0.0-1.1 U/L), TPOA<sub>t</sub> 234 (0.0 - 12 IU/ml), TgA<sub>t</sub> > 2000 (0.0 - 30.0 IU/ml). A diagnosis of Graves' disease was established and therapy with thyrosuppressant, Thiamazole (Thyrozol®, P&G Health Austria GMBH) 20 mg once a day, Propranolol® (Propranolol®, Galenika AD Belgrade) 40 mg 3x1/4, Bromazepam (Bromazepam HF®, Hemofarm AD Vršac) 3 mg in the evening, was started immediately. The finding of pleural punctate on microbiological examination was normal, the pathology finding indicated the presence of cells that corresponded to malignant cells. A multi-detector computed tomography (MDCT) showed a left breast tumor with metastases in the supraclavicular and axillary lymph nodes, infiltration of the tumor into the skin and subcutaneous tissue, as well as metastases in the bones (Figure 3).



**Figure 3.** MDCT of chest in the axial plane before chemotherapy (In the pleural space, there is bilateral pleural effusion, hanging to the left. Heterogeneous soft tissue change was present in the lateral part of the left breast, secondary deposit in the vertebral body of the vertebral column).



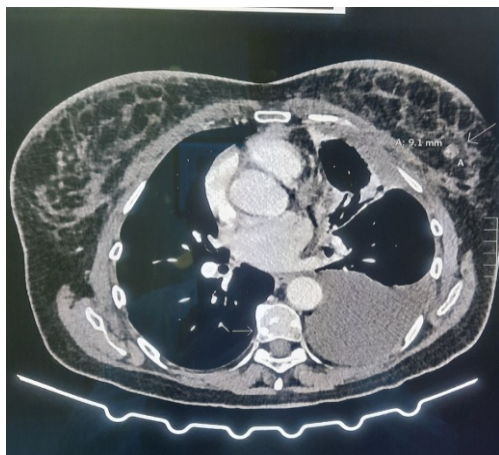
**Figure 4.** Exophthalmos after therapy



**Figure 5.** Mastitis carcinomatosa after chemotherapy

A biopsy of the breast tumor was performed, and PH findings indicated poorly differentiated ductal carcinoma of the breast, HER-2+ group of tumors. Moderate proliferation index Ki-67 = 30% was present, estrogen receptor was negative, progesterone receptor was positive (2%+, score 3). The patient was presented to the oncology council, which prescribed 6 cycles of chemotherapy:TXTR protocol with HER2 blockade (Herceptin+Perjeta). Control

hormonal analysis were: TSH 8.6 (0.3 -5.5 mIU/L), FT4 9.8 (11.5 - 23 pmol/L), TSHRA<sub>t</sub> 5.5 (0.0 - 1.) U/L. The exophthalmos on the eyes decreased (Figure 4), and after 4 cycles of chemotherapy, there was regression in the breast's tumor mass clinical and radiology (Figure 5 and 6), with the withdrawal of effusion. Radiation therapy was also planned after chemotherapy. The patient stated that she subjectively felt better.



**Figure 6.** MDCT of chest in axial plane after chemotherapy (In the pleural space on the left, there is pleural effusion in regression. Also, there is a heterogeneous soft tissue change in the lateral part of the left breast in regression with unmodified secondary deposit in the vertebral body of the vertebral column).

## DISCUSSION

The patient we present stated that before the detection of breast cancer, she did not examine the thyroid gland and that she certainly did not have ophthalmopathy. Both breast morphologies and eye disorders appeared at the same time. Numerous studies unequivocally link hyperthyroidism and breast cancer (17). In patients with Graves' disease, which is basically an autoimmune process, antibodies bind TSH receptors on the surface of thyrocytes and cause their stimulation. The increased concentration of triiodothyronine and tyrosine activates MPAK pathways and causes phosphorylation of estrogen receptors and enhances the proliferation of breast cells, while at the same time inhibiting their process of apoptosis via integrin  $\alpha v\beta 3$  (18 - 19). One possible mechanism is a cross-reaction of autoantibodies in these two tissues, which occurs because of the immunological similarity between lactoperoxidase in the breast and thyroperoxidase in the thyroid gland (20). The effect of TSH itself is achieved through its TSH-R receptors, which are expressed in breast tumors as they activate numerous signaling pathways (21). Govindaraj and colleagues examined the expression of TSH-R in healthy women and women with breast cancer, where their number was significantly increased in the affected population, which could explain the importance of TSH in the development of cancer (22, 23). Studies estimate that

there is a 38% increased risk of breast cancer in patients with hyperthyroidism after 5 - 10 years of the disease, including the subclinical form, which we do not exclude in our patient, as well as in patients after 60 years of age, as is the case with our patient. Patients with hypothyroidism, whose diagnosis was made before the age of 40, are associated with a lower risk of the disease. It is interesting that patients who were treated for hyperthyroidism with radioactive iodine showed an increased frequency of breast cancer compared to a healthy population, or those who were not treated, or treated with thyro-suppressants (24, 25). One study examined the incidence of breast cancer in patients who took thyroid hormone replacement. In a study of 5,505 patients, 635 used therapy, in which the frequency was much higher than in patients without thyroid disease (12.3 vs. 6.2%), especially after the use of drugs for a period longer than 15 years (26). However, in 2017, a meta-analysis was conducted and proved the opposite that there is no correlation between the use of drugs and the occurrence of cancer (27). After the diagnosis of Graves' disease and breast carcinoma in our patient, we immediately started with therapy, both antithyroid drugs (ATDs) and chemotherapy. Numerous studies have been based on examining the effectiveness of ATDs on breast cancer. Back in 1946, Morrison and his collaborators examined the effect of ATDs and induced hypothyroidism on mice and examined their effect on breast. Later, Vonderhaal and his collaborators explained that the hypothyroidism leads to atrophy of the mammary glands. Additional research has shown the effect of ATDs on reducing the proliferation of tumor cells, as well as their necrosis. Also, a study in which mice were inoculated with breast adenocarcinoma was conducted. However, the tumor completely went into remission after mice were treated with propylthiouracil. Based on these facts, it is certainly necessary to consider ATDs as adjuvant therapy in patients with breast cancer (28 - 31).

## CONCLUSION

The most likely one of the possible causes of breast cancer is unrecognized Graves' disease. Similar to estrogen, thyroid hormones also can induce the proliferation of breast cells, and that is why patients with a long history of untreated thyroid disease have an increased risk of BC. There is a possibility that early detection of thyroid disease

would not lead to the development of a malignant process, and that is why doctors in their clinical work must recognize the first signs of thyroid disease in their patients and immediately start with therapy to reduce the potential risk of BC. There is a significant role in using screening tests to discover breast cancer in patients with untreated or inadequately treated hypo- and hyperthyroidism. In addition, it is recommended to determine thyroid

status in all patients with breast cancer, and start therapy if it is necessary.

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#### **Conflict of interest**

All authors declare no conflict of interest

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## Karcinom dojke i Grejvsova bolest

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### SAŽETAK

**Uvod.** Brojna klinička ispitivanja dokazala su povezanost dvaju žlezdanih organa, u ovom slučaju dojke i štitaste žlezde. Pojava karcinoma dojke povećana je kod pacijenata sa autoimunom bolešću štitaste žlezde (Hašimotov tireoiditis i Grejvsova bolest). Broj opisanih slučajeva karcinoma dojke značajno je manji kod pacijenata sa Grejvsovom bolešću nego kod onih sa dijagnostikovanim Hašimotovim tireoiditisom.

**Prikaz slučaja.** Pedesetsedmogodišnja pacijentkinja javila se u Urgentni centar sa teškim disanjem. Prilikom pregleda utvrđeni su oftalmopatija, oslabljen disajni šum i mastitis obeju dojki. Vrednosti analiza hormona bile su sledeće: TSH: 0,00 (0,3–5,5 mIU/L); FT4: 32,90 (11,5–23 pmol/L); TSHRat: 19 (0,0–1,1 U/L); TPOAt: 234 (0,0–12 IU/ml); TgAt: > 2000 (0,0–30,0 IU/ml). Postavljena je dijagnoza Grejvsove bolesti i odmah je započeta terapija tireosupresivom. Multidetektorska kompjuterska tomografija (MDCT) pokazala je tumor leve dojke sa metastazama u supraklavikularnim i aksilarnim limfnim čvorovima, infiltraciju tumora u kožu i potkožno tkivo, kao i metastaze u kostima. Urađena je biopsija tumora dojke, a patohistološki nalaz ukazao je na slabo diferenciran duktalni karcinom dojke (HER-2+ grupa tumora).

**Zaključak.** Rano otkrivanje bolesti štitaste žlezde smanjuje rizik od razvoja malignog procesa; stoga, lekari u svom kliničkom radu moraju prepoznati prve znake bolesti štitaste žlezde kod pacijenata i odmah započeti adekvatnu terapiju kako bi smanjili rizik od nastanka karcinoma dojke. Važno je sprovesti dijagnostička ispitivanja za otkrivanje raka dojke kod pacijenata sa nelečenom ili neadekvatno lečenom hipotireozom i hipertireozom.

**Ključne reči:** karcinom dojke, Grejvsova bolest, autoimuni poremećaji štitaste žlezde