

Case Report

Early-onset breast disease: case of a Grave condition with a favorable prognosis

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Abstract: Background: The relationship between thyroid and breast diseases has been well documented, but the clinical impact of Graves' disease on breast tissue is not clear. Patient Findings: Twenty-seven year-old African American female patient who presented with multiple bilateral breast masses and skin thickening and ulcerations. Biopsy of the breast masses demonstrated fat necrosis. During her initial evaluation, she was found to be hyperthyroid and was ultimately diagnosed with Graves' disease. Her abnormal breast changes resolved within several months of her medical treatment for Graves' disease. Summary: Graves' disease may present with acute-onset breast changes without personal history of trauma or family history of breast abnormalities. Conclusions: Interactions between thyroid and estrogen hormones should be studied further to determine their exact clinical and pathologic implications. Medical or surgical management of Graves' disease may reverse associated pathologic breast changes.

Keywords: Graves' disease, thyroid hormone, estrogen, fat necrosis

Introduction

The relationship between diseases of the breast and thyroid has been previously reported [1-4]. Thyroid hormone is known to impact estrogen-mediated cell growth and dysplasia in breast cancer cell lines as well as patients with breast disease. Few case reports have documented the association of Graves' disease and mastoplasia [2, 3, 5]. Even fewer cases exist in which patients with Graves' disease develop an early-onset breast cancer [6]. However, others reported a higher incidence of breast cancer in patients with Hashimoto's thyroiditis than in patients with Graves' [1, 7, 8]. The association between non-Graves' hyperthyroidism and gynecomastia has been reported as well [9, 10]. Despite these reports, the relationship between thyroid and breast diseases remains controversial [11-14]. In this brief communication, we report one young female patient with bilateral, symmetric fat necrosis of the breasts and overlying skin excoriations. Treatment of Graves' disease in this patient caused complete resolution of her breast changes.

Patient

Twenty-seven year-old African American female, gravida 1, para 1 presented with multiple bilateral breast masses, which according to her description appeared "all of a sudden" two months prior to her initial office visit. The breast masses were associated with skin thickening and unremitting pain, which bore no relationship with her menses. She denied any trauma or nipple discharge. There was no family or personal history of breast disease. However, her maternal grandmother had goiter and her maternal aunt had a total thyroidectomy for an unknown etiology. Her family history was otherwise unremarkable. She denied tobacco and intravenous drug abuse, but drinks alcohol on occasion. The patient reported no fevers, chills, heat or cold intolerance, or chest pains. There were no compressive symptoms including dysphagia, dyspnea, odynophagia, or hoarseness of voice. She did complain of occasional heart palpitations, growing anxiety, and a recent 12-16 pound weight gain over the past month, to which she attributed some mild neck enlarge-

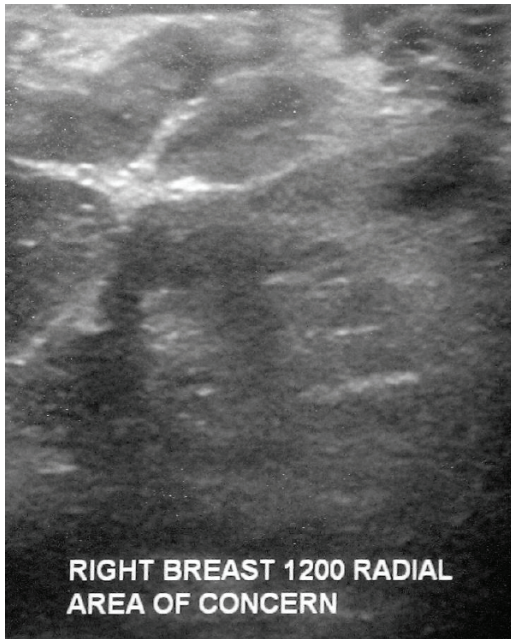


Figure 1. Representative ultrasound image of patient's right breast. Right breast demonstrating hypoechoic (dark) regions which are suspicious for areas of necrosis. Hyperechoic (white) regions are indicative of fibroglandular tissue without evidence of a malignant process.

ment.

She was afebrile and normotensive. Physical examination findings included mild diffuse thyromegaly with no palpable discrete nodules. There was no associated tracheal deviation. There was no palpable lymphadenopathy in central, lateral or posterior compartments of neck. Interestingly, a bruit was present on the thyroid. Breast examination revealed evidence of large, tender, mobile nodules on each breast with overlying skin excoriation. There was no palpable axillary lymphadenopathy. Same-day mammogram and ultrasound were performed and revealed evidence of scattered fibroglandular densities without any suspicious masses, calcifications, skin thickening, or axillary lymphadenopathy (**Figure 1**). Core needle biopsies of each mass showed fat necrosis while the skin biopsy was described as a necrotic ulcer bed. Breast MRI showed nonspecific skin thickening without evidence of abnormal enhancement, mass or other suspicious findings (**Figure 2**). Due to her symptoms suggestive of hyperthyroidism and her family history of total thyroidec-

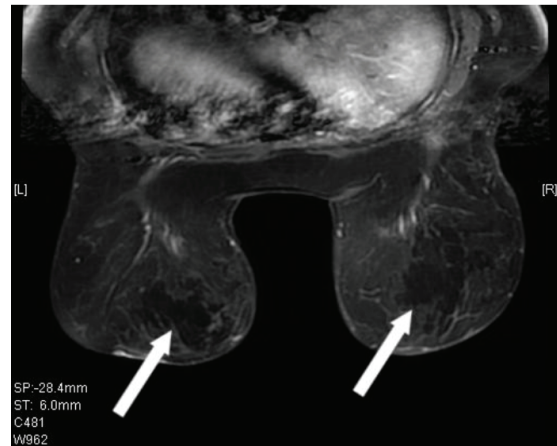


Figure 2. Representative MRI of patient, axial section. Arrows indicate regions of fat necrosis in breasts bilaterally. Axial section at approximately 9th thoracic vertebral level.

tomy, thyroid functions tests and a thyroid ultrasound were performed. Her laboratory workup showed a significantly suppressed thyroid stimulating hormone (TSH) < 0.01 mIU/L (normal = 0.5-5.0) and an elevated free T4 of 18.2 pmol/L (normal = 5-12). A radioactive iodine-131 uptake scan demonstrated diffuse uptake of 50.8% at 4 hours, and 75.0% at 27 hours, suggestive of Graves' disease. She was subsequently diagnosed with Graves' Disease and started on a regimen of methimazole 20 mg/day. Patient breast and skin changes and tenderness improved dramatically and completely resolved after three months of medical management. She has been followed up for four years and remains euthyroid, entirely asymptomatic with normal breast examination.

Discussion

The interaction between thyroid hormone and estrogen-sensitive tissues, notably the breast, has been well documented [15-21]. However, bilateral breast necrosis has never been reported in association with Graves' disease. There are several case reports documenting the association between other breast pathologies such as gynecomastia in patients with hyperthyroidism [9, 10, 22, 23], or breast cancer in patients with autoimmune thyroid disease [1, 4, 7, 8, 24]. One recent case-control study by Xu, et al, even demonstrated an association between differentiated thyroid carcinoma and BRCA1

gene polymorphisms [25]. Interestingly, the treatment of hyperthyroidism in patients with gynecomastia or mastoplasia has been associated with resolution of associated abnormal breast changes. There are only a number of case studies that report the relation of gynecomastia to hyperthyroidism, and each of them document resolution of the breast dysplasia within one year of return to a euthyroid state [3, 9, 10, 23, 26]. In one of the largest case series to date, twelve of fifteen males with hyperthyroid-associated gynecomastia achieved total remission of gynecomastia with the return to a euthyroid state, while the other three showed a significant reduction in breast size [2]. The fact that breast dysplasia can appear simultaneously with thyroid disease and resolve with successful management of the hyperthyroid state can hardly be considered a coincidence.

Because certain diseases of the breast are more associated with autoimmune thyroid phenomena (e.g. breast cancer), whereas other diseases of the breast are associated with any hyperthyroid etiology (e.g. gynecomastia), it is unknown whether the autoimmune nature of thyroid disorders or simply the hyperthyroid state effects these pathological breast changes. If we assume the underlying cause to be elevated thyroid hormone levels, similar downstream signaling pathways and heteromeric nature of steroid hormone receptors allow considerable cross-talk. Estrogen and thyroid hormones utilize the same extranuclear machinery such as mitogen activated protein kinase and phosphoinositol 3-kinase to induce cell proliferation [16]. Triiodothyronine- and tetraiodothyronine are both known to act on the $\alpha\beta3$ integrin receptors in certain tissue types to induce a downstream cascade of events which ultimately activate the estrogen receptor α in the absence of estrogen itself [18]. Thyroid hormone also stimulates estrogen receptors indirectly via heteromerization with activated thyroid receptors, likewise in the absence of estrogen [27]. It is likely that there is no singular mechanism explaining the interaction between thyroid hormone and estrogen, but that there are multiple points of overlap in their signaling pathways. Further studies are necessary to elucidate the complex interaction between these two steroid hormones.

While this information may not sufficiently explain the coincidental onset of bilateral fat ne-

crosis of the breast and Graves' disease in our patient, we believe that the developing hyperthyroidism may have directly contributed to her breast dysplasia. To our knowledge, this is the first reported case of Graves' disease presenting with bilateral fat necrosis of the breast. We propose that the symmetric breast changes in our first patient occurred secondary to proliferating fibroglandular and connective tissue, a process which may have put her breasts at increased risk of injury and could explain her unique breast disease. The fact that her unique breast changes responded to medical treatment within a matter of three months, while extremely fortunate, should not be mistaken for chance. Our patient's acute-onset breast changes presented concomitantly with her hyperthyroidism secondary to Graves', and resolved with the return to euthyroid.

It is imperative that physicians recognize the clinical significance of the interactions between thyroid hormone and estrogen. Because the identification and management of thyroid disease has been reported to reverse associated pathologic breast changes, we recommend thyroid function studies as a routine workup for any patient with unexplained breast dysplasia.

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