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A HORMONE POSITIVE BREAST CANCER MASQUERADING AS CUSHING SYNDROME: A CASE REPORT

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ABSTRACT

Endogenous Cushing syndrome because of ectopic secretion of adrenocorticotropic hormone (ACTH) more commonly arise from small-cell lung carcinoma. Ectopic ACTH secretion from a neuroendocrine tumor of the breast is a rare phenomenon, with only 7 cases previously reported in the literature. We present a case of hormone positive metastatic invasive mucinous carcinoma of breast with neuroendocrine differentiation with multiple metabolic complications.

KEYWORDS

Cushing Syndrome, neuroendocrine differentiation, cancer breast, ectopic ACTH

INTRODUCTION

Endogenous Cushing syndrome is most commonly associated with an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor. Cushing syndrome secondary to ectopic ACTH produced by non-pituitary cancers, include small cell lung cancers, pancreatic islet cell tumors, thymomas, medullary thyroid cancers, hepatic carcinoid tumors and bronchial carcinoid tumors. [1-4]

Ectopic ACTH secretion from breast cancer is rare, and has an association with less than 1% of tumor.[5] The incidence rate of neuroendocrine cells in breast cancer is reported to be of 21.0% (17/81 patients); but surprisingly, none of the 17 showed ACTH expression.[6]

We present a unique case of metastatic breast cancer with neuroendocrine differentiation masquerading as Cushing's Syndrome.

CASE REPORT

A 59-year-old postmenopausal female was referred to us by the endocrinologist in view of rapid weight gain of 2.5 kgs in 5 months, generalized swelling, proximal muscle weakness and extreme fatigue. She was diagnosed with hypertension and diabetes mellitus 6 months ago and was started on appropriate medications. On examination, she had tachycardia and classical cushingoid features such as moon facies, buffalo hump, proximal muscle weakness and anasarca. Her HbA1c was 7.2%. Serum alkaline phosphatase and lactate dehydrogenase levels were raised. ABG showed hypokalemia with mild metabolic alkalosis. Serum Chromogranin levels were raised (419 ng/ml).

Based on the high Serum ACTH value (456 pg/ml) and a normal MRI Pituitary, we performed an overnight dexamethasone suppression test which failed to suppress cortisol.

With consensus decision from endocrinologist and our team, CT chest and abdomen was advised.

The scan showed multiple hypoattenuating liver lesions scattered in both the lobes with largest measuring 12 cm x 5.8 cm with central necrosis and peripheral enhancement, retraction of liver capsule suggestive of metastasis. Incidentally, a soft tissue lesion in the inner quadrant of right breast measuring 1.5 cm was seen. Both the adrenals were bulky with normal enhancement. No focal lesion was seen anywhere else in the body. Patient was unaware of the breast lump. Provisional clinical diagnosis of neuroendocrine tumor was made.

Further workup with DOTA PET CT revealed an irregular spiculated nodular lesion in the upper inner quadrant of the right breast with increased SSTR expression likely representing a primary breast malignancy with neuro-endocrine differentiation. Multiple variable sized hepatic lesions predominantly involving left lobe of liver with SSTR expression and subtle sclerosis with increased SSTR expression involving L4 lumbar vertebra was observed suggesting metastasis. Bilateral mammography showed BIRADS 5 lesion in upper inner quadrant of right breast. In multidisciplinary team discussion, a scenario involving breast malignancy with neuro-endocrine differentiation was considered most likely responsible for Cushing Syndrome, though exceedingly rare.

To confirm the diagnosis, right breast lump core biopsy was recommended. She was diagnosed as ER/PR Positive, CerbB2 negative grade II invasive mucinous carcinoma with neuroendocrine differentiation (Figure 1 and 2).

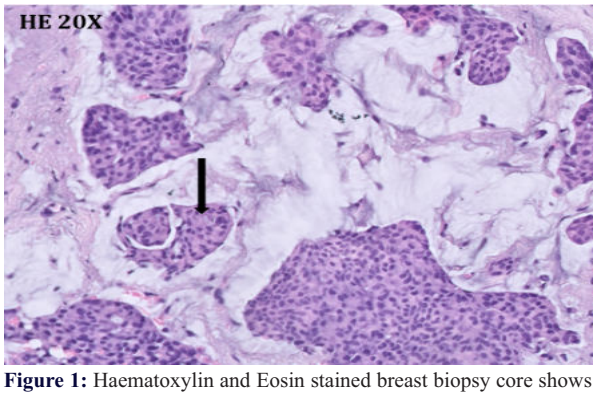

Figure 1: Haematoxylin and Eosin stained breast biopsy core shows tumour cells in nests with a round to oval nucleus and fine chromatin, within a stroma showing mucin pools.

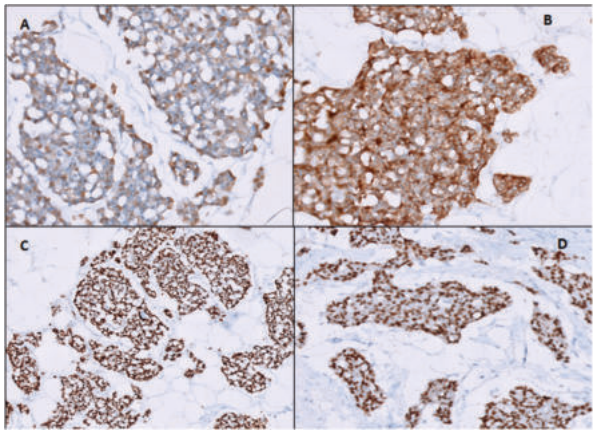

Figure 2: IHC: Tumor cells show cytoplasmic expression of neuroendocrine markers chromogranin A (FIGURE 2A) and synaptophysin (FIGURE 2B) as well as nuclear ER (FIGURE 2C) and PgR (FIGURE 2D).

Thus, the diagnosis of metastatic carcinoma breast with neuro-endocrine differentiation masquerading as Cushing's Syndrome was confirmed. She, was, thus started on hormonal therapy with oral Letrozole 2.5 mg daily and Palbociclib 125 mg daily for 3 weeks and 1 week off which is the standard of care. She was also started on tablet ketoconazole for Cushing syndrome.

Post 2 months of the therapy, the interim DOTA PET-CT scan showed progression of the disease with new lesions in the liver, though the primary showed reduction in activity and size as well (Figure 3 and 4). The patient then was lost to follow up.

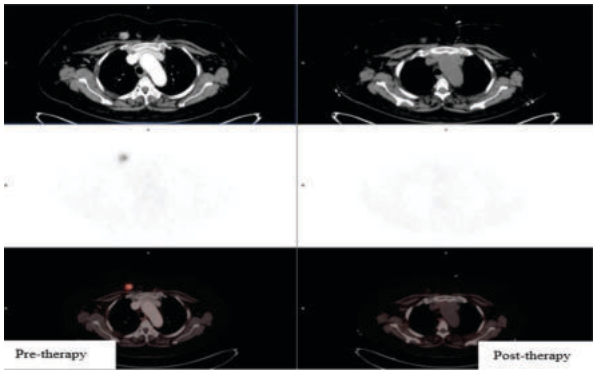

Figure 3: DOTA PET-CT scan shows reduction in the SSTR expression at the primary breast lesion post 2 months of therapy

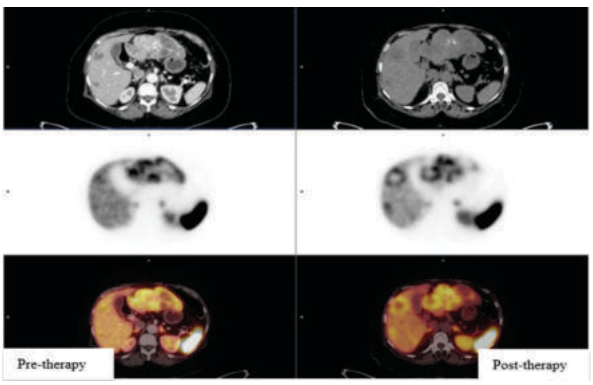

Figure 4: DOTA PET-CT scan shows increased SSTR expression in liver lesions.

DISCUSSION

The most prevalent tumors associated with ectopic ACTH secretion are small cell lung cancer (3.3 to 50%), bronchial carcinoid (5 to 40%), islet cell tumor of the pancreas (7.5 to 25%), thymic carcinoid (5 to 42%), and pheochromocytoma (2.5 to 25%). ACTH secretion has shown association with worse outcomes.

Other neuroendocrine tumors including those of the breast, account for less than 5% of ectopic ACTH secretion. There are 2 described variants of neuroendocrine tumors of the breast .The most common type is a conventional ductal carcinoma of the breast with neuroendocrine cells comprising <50% of the tumor ("ductal carcinoma with neuroendocrine features"). The less common variant is a differentiated neuroendocrine carcinoma of the breast, usually well differentiated (World Health Organization grade I or II), but poorly differentiated (grade III) tumors resembling small cell lung cancer also occur. Neuroendocrine cells stain for synaptophysin and chromogranin, as seen in our case.[6]

Breast cancers with strong positivity for estrogen and progesterone receptors with Cushing syndrome features account for only 1% of the cases, as seen in our case.[5] There are fewer than 10 cases reported in literature. Most such tumors were strongly hormone positive and only one case was found to be triple negative. Our patient like most other cases was hormone positive(strongly ER positive). This phenomenon could be explained by the participation of ACTH in carcinogenesis dependent on steroid hormones.[7]

The prognosis of cancers with ectopic ACTH secretion depends on primary tumor histology and the presence of metastases.[5] Elevated levels of ACTH, advanced tumor stage, high histological grade and triple-negative subtype are poor prognostic factors in such cancers. Our patient presented with all the poor prognostic markers except the triple negative type.

The treatment mainly has a multimodal approach with oncologist and endocrinologist to control growth of tumor and symptoms of Cushing syndrome respectively. Our patient at the time of presentation had metastatic disease with high ACTH and was thus, started on hormonal therapy with tablet letrozole and palbocicilib like most hormone positive breast cancers along with tablet ketoconazole for Cushing syndrome. She unlike other reported cases did not respond well to medical management for Cushing syndrome.

Unlike other reported cases, we choose oral hormonal therapy for the patient as she was strongly hormone positive. However, the patient did not respond to our expectation and later, was lost to follow up to assess the long-term benefit.

CONCLUSION

In conclusion, ectopic ACTH secretion from a breast cancer is extremely rare. However, a patient with Cushing syndrome and high ACTH value should raise a suspicion and be further investigated. Although there are no definitive guidelines for the treatment of this type of presentation, the treatment strategy should be a combination of a personalized oncological management and support treatment for associated hormonal disturbances which is a multidisciplinary approach.

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