Cushing's Storm Secondary to Ectopic ACTH Secreting Metastatic Breast Cancer

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Cushing's Storm Secondary to Ectopic ACTH Secreting Metastatic Breast Cancer

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Objective:

Describe a rare ectopic ACTH secreting breast cancer causing Cushing's syndrome presenting with posterior reversible encephalopathy syndrome (PRES) from uncontrolled hypertension leading to psychosis and liver function abnormalities from liver metastasis, complicated opportunistic infection, and deep vein thrombosis posing unique management issues.

Case Presentation:

A 31 year old female, with triple negative, high grade invasive right breast ductal carcinoma treated with chemotherapy, bilateral mastectomy, and radiation presented with acute psychosis. She had not slept for 4 days, was hyperenergetic, easily distracted, impulsive with racing thoughts, pressured speech and was paranoid that her husband was trying to hurt her. On exam she had round, ruddy, hirsuite face with acne and her blood pressure was 156/108. Labs showed potassium 1.7 mEq/L (normal range 3.7-5.2 mEq/L), random cortisol >70 mcg/dL (normal range 6-23 mcg/dL), 1mg and 8mg overnight dexamethasone tests showed cortisol >100 mcg/dL (normal range <1.8 mcg/dL). She had elevations in AST to 103 IU/L (normal range 10-34 IU/L), ALT 237 IU/L (normal range 8-37 IU/L), ACTH 1173 pg/mL (normal range 9-52 pg/mL), total testosterone 170 ng/dL (normal range 15-70 ng/dL in women), DHEA-S 499 mcg/dL (normal range 45-270 mcg/dL), 17 OH progesterone 1780 ng/dL (normal range <200 ng/dL) and 24 hr urine cortisol (UFC) 14766mcg (normal range 10-100 mcg/24hr). CT abdomen showed extensive hepatic metastatic disease and bilateral adrenal hyperplasia. Renin, aldosterone, plasma metanephrines, chromagranin A, corticotropin releasing hormone, and gastrin levels were normal. Imaging was negative for thyroid nodule, thymic neoplasm, and bronchial carcinoid. Core liver biopsy revealed metastatic breast adenocarcinoma that was negative for neuro endocrine markers CD56, synaptophysin, neuron specific enolase, and chromogranin.

CT head showed white matter disease consistent with PRES. She was psychotic and hypertensive despite using mifepristone with multiple antihypertensives including lisinopril, aldactone, and metoprolol targeting a systolic blood pressure of 110-130. Transaminitis did not allow mifepristone escalation > 600mg/day. Etomidate infusion at a non-sedating dose of 0.1mg/kg/min in the ICU controlled her hypertension and cortisol levels to 20-30 mcg/dL.[1,2,3] UFC reduced to 820mcg. She was transitioned to metyrapone 1250 mg PO Q6h and spironolactone 100 mg PO Q6h.[4,5] Bilateral adrenal resection, which results in permanent adrenal insufficiency and carries a very high risk of mortality, was successfully avoided by medication utilization to block cortisol. Dapsone used for PCP prophylaxis due to bactrim allergy did not prevent PCP pneumonia, but the infection was successfully treated with primaquine. After a long hospital course, with an exceptional care team at LVHN Muhlenberg Hospital consisting of our colleagues in neurology, hematology-oncology, critical care, infectious disease, hospitalist, and pharmacy, she was discharged from the hospital. She continued on metyrapone with spironolactone and is undergoing chemotherapy.

Post hospitalization, she was followed by endocrinology as an outpatient and repeat UFC showed decreased cortisol excretion to 688 mcg/24hr. Serum levels have decreased to 16 mcg/dL. Her lower cortisol level allowed for de-escalation of her metyrapone dose to 500mg PO Q6h and provides useful biochemical evidence of chemotherapuetic success of her breast cancer management. There was improvement in her liver metastases on repeat CT scans, however, she needed denosumab for metastatic bone lesions. She also developed an upper extremity DVT and was started on anticoagulation.[6]

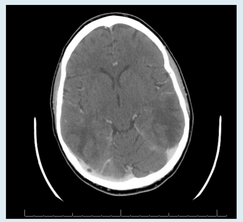

Figure 1. CT head with contrast showing PRES

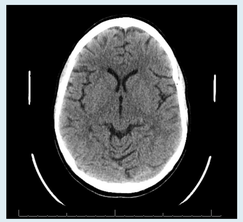

Figure 2. CT head with contrast showing resolution of PRES

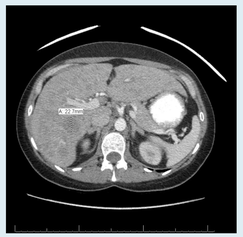

Figure 3. CT abdomen/pelvis showing liver metastases

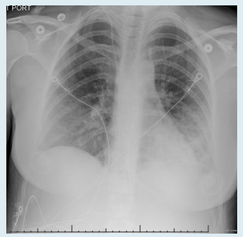

Figure 4. Chest X-ray showing development of LLL consolidation

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Discussion:

Ectopic ACTH Cushing's syndrome from breast cancer is extremely rare.[7,8] The biopsy specimen did not stain for neuroendocrine markers and work up of other etiologies was completely unrevealing. The declining cortisol response requiring metyrapone dose de-escalation following chemo therapeutic intervention strongly suggested breast cancer as the etiology of her Cushing's.

The imaging done for evaluation of her acute psychosis revealed changes consistent with posterior reversible encephalopathy syndrome (PRES) and usually is characterized by hypertensive encephalopathy.[9] PRES associated with Cushing's syndrome has been previously reported only in pediatric patients for which HCTZ and propranolol was used for hypertension management.[10] To the best of our knowledge, this is the first case of adult PRES associated with hypertension from Cushing's ever reported. Initial utilization of intravenous etomidate in the intensive care unit and subsequent transition to oral metyrapone (both of these agents block 11-beta-hydroxylation of deoxycortisol to produce cortisol) and oral spironolactone (to antagonize the mineralocorticoid action of deoxycortisol) successfully controlled her hypertension and prevented recurrence of her psychosis. To the best of our knowledge, this is also the first case of successful treatment of PRES associated with Cushing's using etomidate with metyrapone transition. This strategy also avoided needing bilateral adrenalectomy which is reserved for severe Cushing's patients but carries high mortality.[11,12]

Hypercortisolism causes immunosuppression which not only facilitated rapid relapse of her previously treated breast cancer, but also rendered her susceptible to opportunistic infection with pneumocystis jirovecii pneumonia. Pneumocystis pneumonia has a high mortality, especially in patients with Cushing's, hence its prophylaxis is essential in the management of severe cases of Cushing's. Bactrim, which is the drug of choice of pneumocystis pneumonia prophylaxis, could not be utilized due to severe sulfa allergy, so dapsone was initiated. Pneumocystis pneumonia management in Cushing's was further complicated because glucocorticoid treatment is used as an adjunctive therapy. Rapidly decreasing circulating cortisol levels resulting from etomidate therapy could have potentially worsened her pneumonia. For this reason, a random cortisol level of 40mcg/dL was initially targeted.[13] Despite initiation of dapsone, she developed pneumocystis pneumonia, but subsequently was successfully treated with primaquine.

Conclusion:

Ectopic ACTH Cushing's syndrome from breast cancer is extremely rare, presenting with significant morbidity and mortality from opportunistic infections, psychoses, metabolic, and coagulation derangements. This case reports management of Cushing's psychosis resulting from PRES and hypertension with etomidate followed by metyrapone and spironolactone transition since mifepristone could not be increased in liver dysfunction. Also, it reports successful management of other complications including infections and coagulation, which can be potentially fatal. Ectopic Cushing's syndrome presents unique diagnostic and management challenges.