Case Report

Neuroendocrine Carcinoma of the Breast With Endobronchial Metastases and Syndrome of Inappropriate Antidiuretic Hormone Secretion

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Clinical Practice Points

- We present the case of a woman with neuroendocrine carcinoma of the breast who presented with syndrome of inappropriate antidiuretic hormone secretion, endobronchial metastases, and bone metastases.
- To the best of our knowledge, no cases of primary neuroendocrine cancer of the breast with syndrome of inappropriate antidiuretic hormone secretion and documented endobronchial metastases have been reported.
- Treatment with letrozole and palbociclib resulted in improvement.

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Introduction

Primary neuroendocrine cancer of the breast (NECB) is an uncommonly recognized entity. In 2003, the World Health Organization characterized NECB according to features distinct from those of other breast tumors.[1] Primary NECB was defined by the presence of neuroendocrine markers in > 50% of tumor cells. We present the case of a woman with NECB with syndrome of inappropriate antidiuretic hormone secretion (SIADH), endobronchial metastases, and bone metastases.

Case Report

A 67-year-old woman presented with back pain. The physical examination findings were normal, although the results of a breast examination were not documented. A technetium-99m-methylene diphosphonate bone scan showed abnormal tracer concentrations throughout the axial and appendicular skeleton. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis showed adenopathy in the lower neck, predominantly on the left. Extensive right hilar adenopathy was present, with largest lymph nodes measuring 2.2 × 1.6 cm and 1.7 × 1 cm. A right apical lung mass measured 1.7 × 1 cm, and multiple nodules in both upper lobes measured ≤ 5 mm. Extensive osteoblastic and osteolytic metastases involved the right humerus, scapulae, multiple ribs, multiple thoracic and lumbar vertebrae, and the pelvis. She had developed lethargy, confusion, dyspnea, and cough. The serum sodium level was 118 mmol/L. The urine osmolality was 505 mOsm/kg. The alkaline phosphatase level was 1337 IU/L. The hemoglobin was 10.4 g/dL, and the hematocrit was 30.9%. CT angiography showed no pulmonary thromboembolism. Magnetic resonance imaging of the brain with and without contrast showed calvarial metastases. SIADH was diagnosed and treated. Bronchoscopy showed numerous tumor deposits in the proximal right bronchus but no gross endobronchial tumor or bronchial edema. Bronchial biopsy showed intermediate-grade neuroendocrine carcinoma. Fluorine-18 fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT showed hypermetabolic malignancy concordant with other imaging but also low-grade uptake (standardized uptake value, 2.7) in a region of increased density in the lower inner quadrant of the left breast and low-grade uptake in prominent, not pathologically enlarged level 2 and 3 left axillary lymph nodes. Mammography was not performed. She was treated with 4 cycles of cisplatin 60 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1 to 3 every 28 days. Adjunctive zoledronic acid was given. The hyponatremia resolved. She had a clinical and radiographic response, with near complete resolution of the bulky lower cervical, supraclavicular, mediastinal, and hilar adenopathy and in

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the lung nodules, except for a 7-mm right perihilar nodule. Improvement had occurred in the skeletal metastases, with interval development of sclerotic bone changes. CT of the chest at 4 months showed no interval change.

She was first seen in our clinic 1 year after the diagnosis. She was symptomatic, with right scalp tenderness and bilateral upper leg pain of recent onset. The physical examination findings were notable for a 1-cm hard mass in the right breast. The chemistry panel results were normal. She was mildly anemic, with a hemoglobin of 12.0 g/dL. CT of the chest with contrast enhancement showed 1.2-cm and 4-mm masses in the right breast, interval development of multiple, subcentimeter subcutaneous nodules, and a 7-mm posterolateral right chest wall mass. Interval progression was present in the lungs, with multiple new and enlarging lesions bilaterally, reemergence of left cervical adenopathy, and a 9 × 7-mm left axillary lymph node. Left infrahilar and right paratracheal lymph nodes had increased in size. Skeletal metastases were not significantly changed. Diagnostic mammography and right breast ultrasonography showed a heterogeneously hyperechoic mass in the right breast measuring 1.1 × 0.9 × 1.2 cm and smaller bilateral masses measuring 3 to 8 mm. The bone scan showed axial and appendicular osseous metastases. An octreotide scan showed no scintigraphic uptake. PET/CT scanning showed the primary mass of the right breast to be hypermetabolic.

Ultrasound-guided core biopsy of the right breast mass showed an epithelial neoplasm arranged in nests and trabecular patterns with intervening slender, elongated collagenous stroma resembling a neuroendocrine pattern (Figure 1). The immunohistochemistry (IHC) panel showed strong and diffuse staining of estrogen receptor, progesterone receptor, cytokeratin 7, GATA3 binding protein, and gross cystic disease fluid protein-15. Neuroendocrine markers showed focal positive staining for CD56 (20% of tumor cells), occasional rare cells positive for synaptophysin and negative for chromogranin. The tumor was negative for thyroid transcription factor-1. Biopsy of the first lumbar vertebra showed metastatic neuroendocrine carcinoma with an IHC profile similar to that of the primary NECB. Retrospectively, we reviewed the bronchus biopsies (Figure 2). The IHC profile was similar to that of the primary NECB. HER2 by IHC was not amplified on the breast or vertebral biopsy specimens.

Next-generation sequencing of the tumors from the right breast and bronchus was performed using the OmniSeq^{SM} Comprehensive platform (Buffalo, NY). Both specimens showed mutations of IDH1 c.548A>G (Y183C) and NOTCH c.6170A>G (Q2057R). The variant allele frequency was approximately 50%, suggesting single nucleotide polymorphisms. No translocations or activating mutations involving *EGFR*, *KRAS*, *BRAF*, *ALK*, *RET*, or *ROS1* were found. Next-generation sequencing of tumors of the breast and bronchus showed mutations that appeared to be normal variants and could not distinguish the primary cancer and metastasis.

We initiated treatment with letrozole 2.5 mg daily and palbociclib 125 mg on days 1 to 21 every 28 days with adjunctive zoledronic acid. The treatment was well tolerated. Her skeletal pain resolved and the serum sodium level remained normal. PET/CT after 3 months treatment showed a decrease in size and abnormal FDG uptake within the right breast and a decrease of abnormal FDG uptake in mixed lytic/sclerotic skeletal metastases. No other sites of disease were identified. The cancer antigen 27.29 tumor marker decreased from 115.9 to 60.1 U/mL.

Discussion

The present case report highlights the clinical presentation, diagnostic challenges, and treatment of NECB. Our patient presented with skeletal, endobronchial, lung, and nodal metastases. She

Figure 1 Histologic and Immunohistochemistry Images of Primary Neuroendocrine Cancer of the Breast. Hematoxylin and Eosin Stain Showing (A) Typical Neuroendocrine Growth Pattern; (B) Strong and Diffuse Staining for Estrogen Receptor; (C) Strong and Diffuse Staining for GATA3 Binding Protein; (D) Moderate and Diffuse Staining for Gross Cystic Disease Fluid Protein 15; and (E) Approximately 20% of Tumor Cells Were Positive for CD56. Original Magnification ×10 for All