A 63-Year-Old Woman With Rash and Proximal Muscle Weakness

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A 63-year-old woman with a history of infiltrating ductal breast cancer, status post-mastectomy and chemotherapy, was in remission for 18 months prior to being admitted to the hospital with complaints of a pruritic erythematous macular rash involving her head, chest, and bilateral upper and lower extremities. Along with the dermatologic manifestations, physical exam revealed proximal symmetrical muscle weakness and bilateral axillary lymphadenopathy. Initial workup for muscle weakness revealed a creatine kinase of 2,200 IU/L (normal 20-180 IU/L). After administration of intravenous fluids for renal protection, serum sodium dropped to 121 mEq/L (normal 135-145 mEq/L). Computed tomography of the chest showed axillary and supraclavicular lymphadenopathy. Biopsy of a supraclavicular node revealed infiltrating ductal cancer with histologic and morphologic characteristics similar to her previous breast cancer. Following an extensive laboratory workup, we concluded that our patient's myositis and hyponatremia were paraneoplastic syndromes secondary to her recurrent breast cancer.

CASE PRESENTATION

A 63-year-old woman with a history of hypertension, hypothyroidism, and stage IIB poorly differentiated infiltrating ductal breast cancer (hormone receptor and Her2/neu negative) that had been in remission for 18 months following left mastectomy and chemotherapy presented to the emergency department with an acute pruritic erythematous macular rash (Figure 1). The rash had progressively worsened over the past three weeks and involved her head, chest, and bilateral upper and lower extremities. Associated symptoms included worsening fatigue, body cramps, and muscle weakness. Along with this rash, symmetrical proximal muscle weakness and bilateral painless axillary lymph node enlargement were noted on physical exam. A rheumatologic panel revealed a positive ANA. She was negative for Anti-SSA/SSB, Anti-DNA, Anti-sm, Anti-nRNP, Anti-Jo-1, Anti-histone, and Anti-Scl-70. Hepatitis panel was also negative, and complement C3 and C4 levels were normal. Creatine kinase (CK) was elevated at 2200 IU/L (normal 20-180 IU/L). She had no recent history of new medications known to cause an elevated CK, nor recent trauma, ethanol, or illicit drug use. Based on the new onset of rash, proximal muscle weakness, and elevated CK, a clinical diagnosis of dermatomyositis was suspected. Shortly after initiation of intravenous fluids for renal protection, serial metabolic panels revealed hyponatremia at a level as low as 121 mEq/L (normal 135-145 mEq/L). The patient was in a euvoletic state, with normal kidney and liver function studies, and had no signs or symptoms to suggest heart failure. Serum osmolality was 260 mOsm/kg (normal 275-295 mOsm/kg), urine osmolality was 674 mOsm/kg (normal 50-1200 mOsm/kg), urine sodium was 155 mEq/L, and TSH was 1.78 IU/ml (normal 0.40-4.00 IU/ml). She was not on any medications known to cause antidiuretic hormone release, and there were no clinical features to suggest adrenal insufficiency. With the above findings, the cause of hyponatremia was determined to be SIADH. The hyponatremia improved with fluid restriction.

Concern for an underlying malignant process prompted a computed tomography scan (CT) of the chest, which revealed bilateral axillary and supraclavicular lymphadenopathy (Figure 2). A biopsy of her supraclavicular lymph node confirmed the diagnosis of a high-grade carcinoma, which was hormone receptor and Her2/neu-negative like her previous cancer and shared the same histologic morphology. MRI of the brain did not demonstrate metastatic disease. Skin biopsy was negative for malignant cells but revealed inflammatory changes characteristic of dermatomyositis (Figure 3).
Prior to discharge, she was started on high-dose prednisone, which mildly improved her skin lesions and muscle weakness. Shortly after discharge, she followed up with oncology and chemotherapy consisting of carboplatin and gemtabbine was initiated. After several cycles of chemotherapy, positron emission tomography showed progression of metastatic lymphadenopathy with new hypermetabolic retroperitoneal lymph nodes. Several months later, her symptoms of muscle weakness progressively worsened along with her performance status, and she passed away while under the care of home hospice.

**DISCUSSION**

Paraneoplastic syndromes associated with breast cancer are uncommon. There have been several reports that discuss myositis associated with breast cancer and a few cases of SIADH associated with breast cancer. To our knowledge, this is the first report describing SIADH and dermatomyositis simultaneously as paraneoplastic syndromes with recurrent breast cancer. Occurrence of these concurrent paraneoplastic syndromes in recurrent breast cancer is rare, and therefore, we can only speculate about their prognostic impact on staging or treatment of recurrent malignancy.

Myositis associated with malignancy includes dermatomyositis and polymyositis. Dermatomyositis presents with proximal muscle weakness and skin changes with classic findings of a heliotrope rash andGottron papules. The pathophysiology of dermatomyositis associated with cancer is not clearly understood; however, it is likely multifactorial. The main contributing factor is thought to be an immune system imbalance with a failure in immunological surveillance. Polymyositis and dermatomyositis associated with malignancy typically occur in adults, with an incidence peak from age 40 to 60 years. In 60% of cases, they precede the clinical onset of neoplasm. Lung, prostatic, and gastrointestinal cancers are the most frequently associated neoplasms in men, while breast and gynecological cancers are most often associated in women. The Bohan and Peter criteria are most widely used to make the diagnosis of dermatomyositis. These criteria take into consideration the physical findings of symmetrical proximal muscle weakness, elevated skeletal muscle enzyme levels, myopathic changes on electromyography, and skin lesions characteristic of dermatomyositis. Meeting all four of the above criteria indicates a definite diagnosis, three out of four a probable diagnosis, and two out of four a possible diagnosis of disease. Skin and muscle biopsy is also helpful in making the diagnosis, with hallmark features of perifascicular atrophic regeneration, degenerating myofibers, and the presence of perivascular inflammation in the muscle. Treatment of this paraneoplastic syndrome is directed towards the underlying cancer. However, as seen in our patient, steroids have been shown to provide some symptomatic relief. If there is a poor response to steroids, immunomodulating therapy may be warranted.

Paraneoplastic SIADH arises from tumor cell production of antidiuretic hormone and atrial natriuretic peptide. Antidiuretic hormone leads to increased free-water reabsorption, whereas atrial natriuretic peptide has natriuretic and antidiuretic properties. These combined actions lead to a hypoosmotic, euvoletic hyponatremia. Common symptoms are nonspecific and include muscle cramps, lethargy, nausea, vomiting, gait disturbances, seizures, and altered mental status. SIADH affects 1% to 2% of all patients with cancer, with small cell lung cancer accounting for most of these cases. SIADH rarely occurs in breast cancer. The diagnosis is one of exclusion and includes a euvoletic state, low serum osmolality, and a urine osmolality greater than appropriate considering the plasma tonicity. Before making the diagnosis, it is essential to rule out other causes of euvoletic hyponatremia such as hypothyroidism, adrenal insufficiency, primary polydipsia, or drug-associated anti-diuretic release. The mainstay treatment of mild to moderate hyponatremia in SIADH is water restriction. Five hundred to 1,000 ml of free water restriction per day.
Figure 2: CT of the chest with contrast showing abnormal appearing adenopathy seen within the bilateral axillary regions in coronal cuts (A&B) and a sagittal view (C). Arrows measure the short axis of the lymph nodes.

is sufficient to correct hyponatremia. When life threatening conditions such as seizures, cerebral edema, or coma are present, treatment with hypertonic saline is indicated. When administering 3% saline, serum sodium levels must be monitored closely, and the correction should be gradual (<10 mEq/day) due to the risk of osmotic demyelination. If sodium levels are resistant to the above measures, demeclocycline is a therapeutic option. This medication interferes with the anti-diuretic hormone effects on the kidney; however, its effects are sometimes unpredictable and it has numerous side effects. Newer pharmacologic agents of interest that have been studied in euvoletic and hypervolemic hyponatremia are vasopressin-2 receptor blockers, referred to as aquaretics. These drugs are competitive inhibitors of vasopressin, with the effective dose dependent on vasopressin serum levels. Vasopressin levels are often unknown and not constant. With the potential for overdiuresis or inadequate diuresis, serum sodium must be monitored closely in this setting.
CONCLUSION

A combination of paraneoplastic syndromes as the presenting signs of recurrent breast cancer has not been well documented. Further studies concerning the relationship of recurrent breast cancer with the development of paraneoplastic syndrome are warranted.

REFERENCES


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