Paraneoplastic SIADH and Dermatomyositis in Cervical Cancer: A Case Report and Literature Review

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Key Words

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Abstract

We present the first known case of a patient with cervical squamous cell carcinoma complicated by paraneoplastic syndromes of both dermatomyositis and inappropriate secretion of antidiuretic hormone (SIADH). The patient in this case presented with generalized body pain and vaginal bleeding. Her cervical cancer was diagnosed as stage IIB by physical exam, imaging, and cervical biopsy, her dermatomyositis was confirmed by muscle and skin biopsy, and her SIADH was diagnosed based on laboratory findings.

Background

Paraneoplastic syndromes are rare disorders of malignancy that cannot be attributed to direct extension of the primary tumor or metastasis, but result from an altered immune response to the neoplasm. These syndromes have been reported in nearly all biological systems and in association with most types of tumor. Primary tumors most commonly associated with paraneoplastic syndromes include small-cell lung carcinoma, ovarian carcinoma, lymphoma, and breast carcinoma [1].

Dermatomyositis is an inflammatory myopathy that has a well-recognized association with several types of cancers, most notably ovarian, lung, pancreatic, stomach, colorectal, and non-Hodgkin lymphoma. In a multinational study of 618 cases of dermatomyositis, only 2 were associated with cases of squamous cell carcinoma of the cervix [2]. A

literature search revealed few other cases of dermatomyositis occurring with cervical squamous cell carcinoma.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been commonly associated with small cell carcinoma, but has only rarely been reported in association with squamous cell carcinoma, and the mechanism for this association is unknown [3]. SIADH in cervical cancer is even more rare. As of 2009, SIADH has been associated with squamous cell carcinomas of various sites of the head, neck, and respiratory tract, but only 1 case involving squamous cell carcinoma of the cervix, and SIADH in that case manifested itself after chemotherapy, a known trigger of the disorder [4]. Only 2 cases of SIADH have been reported in patients with small cell carcinoma of the cervix [5].

We present here the first known case of a patient with cervical squamous cell carcinoma complicated by paraneoplastic syndromes of both dermatomyositis and inappropriate secretion of antidiuretic hormone (SIADH).

Case Presentation

A 52-year-old African American female, who was not having routine pap smears, came to the emergency room with a 1-week history of generalized body pain, weakness, and vaginal bleeding. She complained of ‘aching’ pain and weakness that began in her hands and progressed to her arms and legs. She reported the pain and weakness to be worse on her left side. She complained of more proximal than distal weakness and rated the pain as 8 out of 10. She had been taking ibuprofen (Advil) which provided moderate relief. The pain was made worse with activities involving the use of her upper body.

The patient’s past surgical history was significant only for a tubal ligation and tonsillectomy, 30 and 39 years prior, respectively. Besides acetaminophen (Tylenol), the patient reported taking calcium carbonate (Os-cal) and docusate (Colace). She had no known drug allergies. She reported no alcohol consumption, but smoked half a pack of cigarettes per day. Her family and personal history were negative for cancer. Physical examination was significant for weakness in the upper extremities with 3+/5 motor strength. Her lower extremity motor strength was 5/5.

She was scheduled for urgent evaluation in the gynecology clinic, where a gynecologic exam revealed a 7-cm exophytic cervical mass with question of left parametrial invasion. Endometrial and cervical biopsies were taken and a CT scan of her abdomen and pelvis with contrast was ordered. The patient was admitted secondary to her reportedly severe muscle weakness and pending biopsy results. Routine laboratory workup was initiated.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review from the Editor-in-Chief of this journal.

Pretreatment Investigation

Hematology, Chemistry, and Urine Tests

A basic metabolic panel revealed sodium 123 mmol/l, chloride 89 mmol/l, potassium 3.6 mmol/l, magnesium 2.3 mmol/l, calcium 8.1 mg/dl, phosphorus 3.8 mg/dl, and P_{Osm} 266 mOsm/kg. Other chemistry tests showed glucose (random) 113 mg/dl, creatinine 0.4 mg/dl, BUN 14 mg/dl, total proteins 5.1 g/dl (albumin 2.4 g/dl), total bilirubin 0.5 mg/dl (direct bilirubin 0.2 mg/dl), SGOT (AST) 272 IU/l, SGPT (ALT) 123 IU/l, ALP 93 IU/l, CK 8,404 U/l. Hematology showed Hct 28.8 g/dl, WBC 16.6/μl (65% neutrophils), Hgb 9.5 g/dl, and PLT 365,000/mm³. Urine specific gravity was found to be >1.050.

Pathology

Cervical biopsy revealed a high-grade squamous epithelial lesion (CIN III) with a focus suspicious of invasion. Endometrial biopsy showed moderately differentiated invasive squamous cell carcinoma. The endometrium itself was not seen.

Imaging

A CT of the abdomen and pelvis with contrast revealed an enlarged cervix with a soft-tissue mass consistent with the diagnosis of cervical carcinoma. Also noted were bilateral iliac chain and left periaortic enlarged lymph nodes. Her chest film was not suspicious for neoplasm.

Working Diagnosis

Her history and physical examination as well as imaging and pathology strongly suggested a tumor with parametrial invasion which characterized stage IIB (T2bN0M0) squamous cell carcinoma of the cervix. Laboratory findings of extreme hyponatremia with hyponatremia, hypochloremia, hypocalcemia, decreased plasma osmolality, and increased urine specific gravity were characteristic of SIADH, likely paraneoplastic, related to her cervical carcinoma. The patient's arm and leg pain and weakness along with her elevated creatine kinase were characteristic of an inflammatory myopathy, possibly polymyositis or dermatomyositis, both of which may appear as an early sign of malignancy [2].

Planning and Treatment

Although concurrent chemo-RT with cisplatin was the recommended treatment for stage IIB cervical cancer, the patient was felt not to be a candidate for chemotherapy secondary to her SIADH, a known side effect of chemotherapy [6]. After discussing treatment options with the patient, she opted for external beam radiation therapy (EBRT), and 25 fractions of EBRT to the whole pelvis to a total dose of 4,500 cGy were initiated shortly thereafter. Biopsies of her left deltoid muscle (fig. 1) and skin as well as an electromyography (EMG) were ordered to investigate the cause of the patient's muscle pain and weakness. Fluid restriction was initiated in an attempt to correct her hyponatremia.

Intra- and Posttreatment Investigation

Testing and Pathology Results

EMG showed myopathic potentials with low amplitude and short duration, consistent with myositis. Analysis of the left shoulder skin biopsy was suggestive of systemic inflammatory autoimmune disease. Sections showed dermal fibrosis with a perivascular mild lymphocytic infiltrate with rare eosinophils, slight epidermal atrophy, and focal vascular inflammation. Immunofluorescence studies of the sample revealed +2 linear deposits of fibrinogen around the adnexa. These changes could be seen in dermatomyositis or systemic lupus erythematosus.

Analysis of the left deltoid muscle biopsy showed IgM +2, C3D +3, and fibrinogen +4 deposits around the medium-sized vessels between muscle bundles which were indicative of vascular inflammation of medium-sized vessels. There was striking perifascicular atrophy (fig. 1), a finding typically seen in dermatomyositis and not seen in polymyositis or inclusion-body myositis [7]. Also evident was the expression of MHC class I antigen on muscle sarcolemmal membranes throughout the specimen (fig. 2), a finding that confirmed an inflammatory condition of the muscle.

Based on neuropathology, immunofluorescence, and biopsy results, the most likely diagnosis was dermatomyositis with small vessel vasculitis, secondary to cervical carcinoma.

Clinical Course

Over the course of the patient's hospital stay, her metabolic panel began to return to normal. Within 1 month of admission, her serum sodium level had returned to normal. Upon initiation of radiation

therapy, her muscle pain and weakness began to improve. One month after completion of the radiation treatment, her physical examination was significant for an upper extremities motor strength of 4+/5 bilaterally and a CK of 2,989 U/l.

Discussion

Dermatomyositis is a rare inflammatory myopathy with an unknown etiology that affects females with greater frequency than males. It most commonly presents as a progressive proximal muscle weakness with heliotropic rash. The rash is generally purple and involves the face, eyelids, and other sun-exposed areas of the body, but may be difficult to appreciate in patients with dark skin color. Scalp lesions over the knuckles, called Gottron's papules, are sometimes seen. Elevation of muscle enzymes, such as creatine kinase, is the most sensitive test for inflammatory myositis. EMG is commonly used to rule out other causes of muscle weakness, and the diagnosis is confirmed by muscle biopsy. The association of dermatomyositis and various types of malignancies has been well documented, and it has been estimated that 25–50% of adult patients have an underlying malignancy [8]. Another inflammatory myopathy commonly associated with malignancy is polymyositis. As with dermatomyositis, polymyositis presents with progressive proximal muscle weakness, but the patient typically does not have a rash. Muscle biopsy confirms the diagnosis of one entity over the other, with perifascicular accentuation of fiber changes, including perifascicular atrophy (a diagnostic feature of dermatomyositis), distinguishing it from polymyositis, in which fiber changes are dispersed throughout the muscle fascicles, without a perifascicular accentuation.

SIADH is a condition where the release and/or activity of antidiuretic hormone (ADH) is increased beyond the physiologically expected amount. The excess ADH interferes with renal excretion of water, resulting in hyponatremia and concentrated urine. Neuropsychiatric disorders, a wide range of drugs including chemotherapeutics, anesthetics, and neuropsychiatric drugs, and various lung diseases and pulmonary interventions such as positive pressure ventilation have been identified as causes of SIADH. SIADH also has a documented association with various types of malignancies, most notably small cell carcinoma of the lung. Symptoms of hyponatremia usually begin when a patient's serum sodium level drops below 125–130 mmol/l. These symptoms are usually neurological and include nausea and malaise. As serum sodium continues to fall below 115 mmol/l, the patient may experience headache, altered mental status, seizures, coma, and respiratory arrest [6]. SIADH is diagnosed in patients with hyponatremia and low serum osmolality, but with increased urinary sodium, osmolality, and/or specific gravity.

Our patient presented with progressive, proximal, and bilateral muscle weakness, the cardinal musculoskeletal symptoms of an inflammatory myopathy such as polymyositis or dermatomyositis. Although she did not appear with the classic heliotropic rash characteristic of dermatomyositis, her dark skin pigmentation may have made any skin discoloration difficult to appreciate; therefore both conditions remained in the differential. Nonspecific myopathy was suggested by EMG, and muscle and skin biopsy confirmed the diagnosis of dermatomyositis. In addition, dermatomyositis typically is accompanied by a small vessel vasculitis, as seen in this patient.

SIADH was diagnosed in this patient on the basis of her hyponatremia, low plasma osmolality, and increased urine specific gravity. Although the patient's hyponatremia was severe, the patient did not develop obvious neurological symptoms. The patient had no history of neuropsychiatric disorders, lung diseases or interventions, or medication use

that has been associated with SIADH. In addition, her chest X-ray showed no signs of lung cancer and her workup provided no evidence of another primary malignancy. Even with these findings, it is possible that the patient could have a malignancy other than squamous cell carcinoma of the cervix that was causing her SIADH and dermatomyositis, but her presentation strongly suggests cervical cancer as the cause of these conditions because the symptoms began around the same time as her cervical cancer symptoms and began to resolve upon treatment of that cancer. Additionally, there is a lack of other explanations for either condition.

Conclusions

This patient presents an interesting example of multiple paraneoplastic syndromes occurring in the context of a primary malignancy not generally associated with paraneoplastic syndromes of this kind. This case supports previous findings that treatment of the primary malignancy is the best course of action [1].

Fig. 1. Perifascicular atrophy, a diagnostic finding in dermatomyositis. Muscle fibers at the periphery of the fascicles are small and discolored gray, while those deeper within the fascicles are larger, with the normal green stain. Engel's modified Gomori trichrome stain, $\times 4$.

Fig. 2. Immunocytochemistry using an antibody to major histocompatibility class I (MHC class I, HLAabc, Dako): **a** Normal control muscle, with staining of capillaries only, with no staining of sarcolemma of muscle fibers. **b** Case muscle, with strong staining of sarcolemma of fibers and also of sarcoplasm, with some perifascicular atrophy as well. Both frozen sections, diaminobenzidine (brown) chromogen, Dako Envision Plus system, with light hematoxylin counterstain, $\times 10$.

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