CASE REPORT

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Paraneoplastic Severe Sensorimotor Axonal Polyneuropathy in Pancreatic Neuroendocrine Carcinoma: A Case Report and Review of the Literature

ABSTRACT

Objective: Paraneoplastic neurological syndromes (PNSs) are a diverse group of neurological disorders affecting any part of the nervous system before or during cancer.

Case: A 78-year-old man first experienced pain and burning in the upper extremity three years previously, to which muscle weakness was added a short time later. The same symptoms developed in the lower extremities one year previously. He was admitted to the intensive care unit due to pneumonia and was conscious but quadriplegic with a modified Rankin score of 5. Abdominal computed tomography showed mass lesions in the liver and pancreas. Biopsies revealed pancreatic small cell neuroendocrine carcinoma. Electrophysiological studies revealed severe sensorimotor axonal polyneuropathy. Paraneoplastic sensorimotor axonal polyneuropathy was diagnosed since other causes of polyneuropathy had been excluded. Palliative care was considered due to the patient's poor functional state.

Conclusions: Early diagnosis of cancer is of paramount importance in patients with PNSs if appropriate treatment is to be provided.

Keywords: Neuroendocrine Carcinoma, Quadriplegia, Ki67, Paraneoplastic Neurological Syndromes.

Pankreatik Nöroendokrin Karsinomda Paraneoplastik Ciddi Sensorimotor Aksonal Polinöropati: Vaka Sunumu ve Literatür Taraması

ÖZET

Amaç: Paraneoplastik nörolojik sendromlar (PNSs), kanser öncesi veya kanser sırasında gelişen, sinir sisteminin herhangi bir kısmını etkileyen çeşitli nörolojik hastalıkları içermektedir.

Vaka: Yetmiş sekiz yaşında erkek hastanın üç yıl önce üst ekstremitelerde ağrı ve yanma hissi şikayetleri başlamış ve kısa süre sonra kas güçsüzlüğü eklenmiş. Bir yıl önce de alt ekstremitelerde benzer şikayetler ortaya çıkmış. Yoğun bakım ünitesine pnömoni tansıyla yatırılan hastanın yatış esnasında bilinci açık, fakat kuadriplejik ve modifiye Rankin skoru 5 idi. Abdomen bilgisayarlı tomografi karaciğer ve pankreasta kitle lezyonlarının olduğunu gösterdi. Lezyonyonlardan alınan biyopsiler pankreas orjinli küçük hücreli nöroendokrin karsinom olarak raporlandı. Elektrofizyolojik testler ciddi sensorimotor aksonal polinöropati ile uyumluluk gösteriyordu Diğer polinöropati nedenleri dışlandıktan sonra, hastaya paraneoplastik sensorimotor aksonal polinöropati tanısı konuldu. Hastanın fonksiyonel kapasitesi düşük olduğundan palyatif tedavi planlandı.

Sonuç: PNS'li hastalarda uygun tedavinin başlanması için erken kanser tanısının konulması önem arz etmektedir.

Anahtar Kelimeler: Nöroendokrin Karsinom, Kuadripleji, Ki67, Paraneoplastik Nörolojik Sendromlar.

INTRODUCTION

Paraneoplastic neurological syndromes (PNSs) include a heterogeneous group of disorders developing prior or during cancer due to remote effects of the tumor on the nervous system, but are not related to tumor infiltration, chemotherapy, or metastasis (1,2). PNSs are seen in less than 1% of patients with cancer (3). The expression of various neuronal proteins by cancer cells triggers an immune response misdirected to the nervous system (3). PNSs can affect the central, peripheral, or autonomic nervous systems. Although lung cancer is commonly encountered in patients with PNSs, many cancers within the body can lead to immunological reactions against the nervous system (2,3). Other etiologies of neurological disorders should be ruled out before diagnosis of PNSs, such as nutritional deficiency, vascular insults, infections, toxic substance exposures, medication side-effects, and metabolic derangement (2).

Neuroendocrine neoplasms (NENs) are uncommon, but can occur in various parts of the body, such as the lung, small intestine, stomach, pancreas, large intestine, central nervous system, and thymus (4,5). NENs from the bronchopulmonary and gastroenteropancreatic organs account for over 90% of all cases (4). More than half of extrapulmonary NENs occur in the digestive tract. NENs consist of two families, well-differentiated (low-grade to intermediate-grade) NENs, known as neuroendocrine tumors, and poorly differentiated (high grade) NENs, known as neuroendocrine carcinomas (NECs). Since most gastroenteropancreatic NECs are clinically silent, early detection is difficult. Metastatic disease at diagnosis is reported in 50% to 70% of patients (5). We describe a patient with quadriplegia who was admitted to the intensive care unit (ICU) due to respiratory failure and diagnosed with paraneoplastic sensorimotor axonal polyneuropathy in association with metastatic pancreatic small cell NEC.

CASE REPORT

A 78-year-old man was admitted to the hospital due to cough and sputum persisting for 10 days. The patient was intubated 24 hours subsequently due to respiratory failure and was admitted to the ICU. His history revealed a percutaneous coronary intervention 10 years previously, right and left carpal tunnel release operations two years previously, and a diagnosis of axonal polyneuropathy one year previously. He first experienced pain and burning in the upper extremities approximately three years previously, with muscle weakness being added to the symptoms shortly thereafter. The same symptoms developed in the lower extremities one year previously. The symptoms, especially muscle weakness, were progressive, and the patient had become dependent in daily living. He had been unable to walk without assistance for the previous six months and became completely bedridden in the preceding week. He had not benefited from the right and left carpal tunnel release surgeries, vitamin medications, or physiotherapy. In the ICU, he was conscious but was unable to move any of his extremities. His modified Rankin score (mRS) was 5 with no deep tendon reflexes. There were no signs of facial asymmetry or local neurological abnormalities. His leukocyte count and C-reactive protein level were $21.1x10^9$/L (normal, $4\text{-}12x10^9$/L) and 2.8 mg/dL (normal, <0.5 mg/dL), respectively. Other laboratory test results including hemoglobin, platelet, vitamin B12, folic acid, hemoglobin A1c, liver and kidney function tests, and thyroid hormone levels were within normal limits. Human immunodeficiency virus, hepatitis virus C and B, severe acute respiratory syndrome coronavirus-2, protein electrophoresis, and blood smear studies were unremarkable. Cranial and lumbar magnetic resonance imaging (MRI) was normal. Chest computed tomography (CT) showed right lung pneumonia with no mass lesion. Abdominal CT showed three lesions in the liver, 11x9.2 cm, 3.3x3.2 cm, and 2.1x2 cm in size (Fig. 1a). A 2.6x2.4 cm lesion of a cystic nature was noted in the head of the pancreas (Fig. 1b).

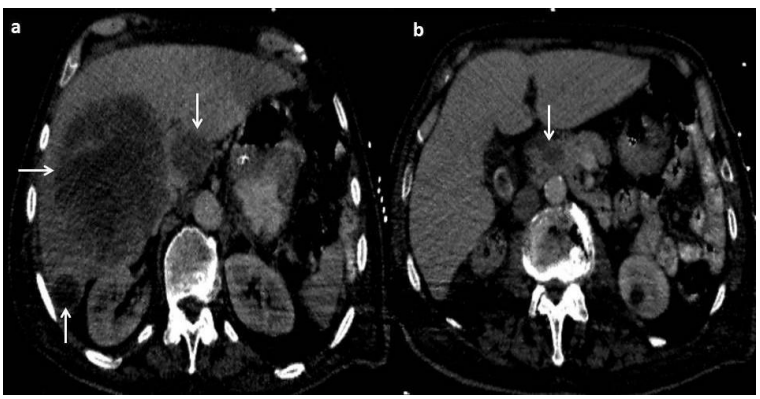

Figure 1. Abdominal CT showing three metastatic lesions in the liver (a, white arrows), and a lesion of a cystic nature in the head of the pancreas (b, white arrow).

Upper and lower gastrointestinal endoscopies and testicular ultrasonography were normal. CT guided-pancreas and ultrasonography guided-liver biopsies showed that the tumor tissues were composed of cells arranged in irregular cords and nest-like groups with scant cytoplasm, and finely dark and granular chromatin (Fig. 2a). Nuclear molding and focal necrosis were observed. The tumor exhibited strong positivity with chromogranin A and CD56 (Fig. 2b, Fig. 2c). The Ki-67 proliferation index was greater than 55% (Fig. 2d).

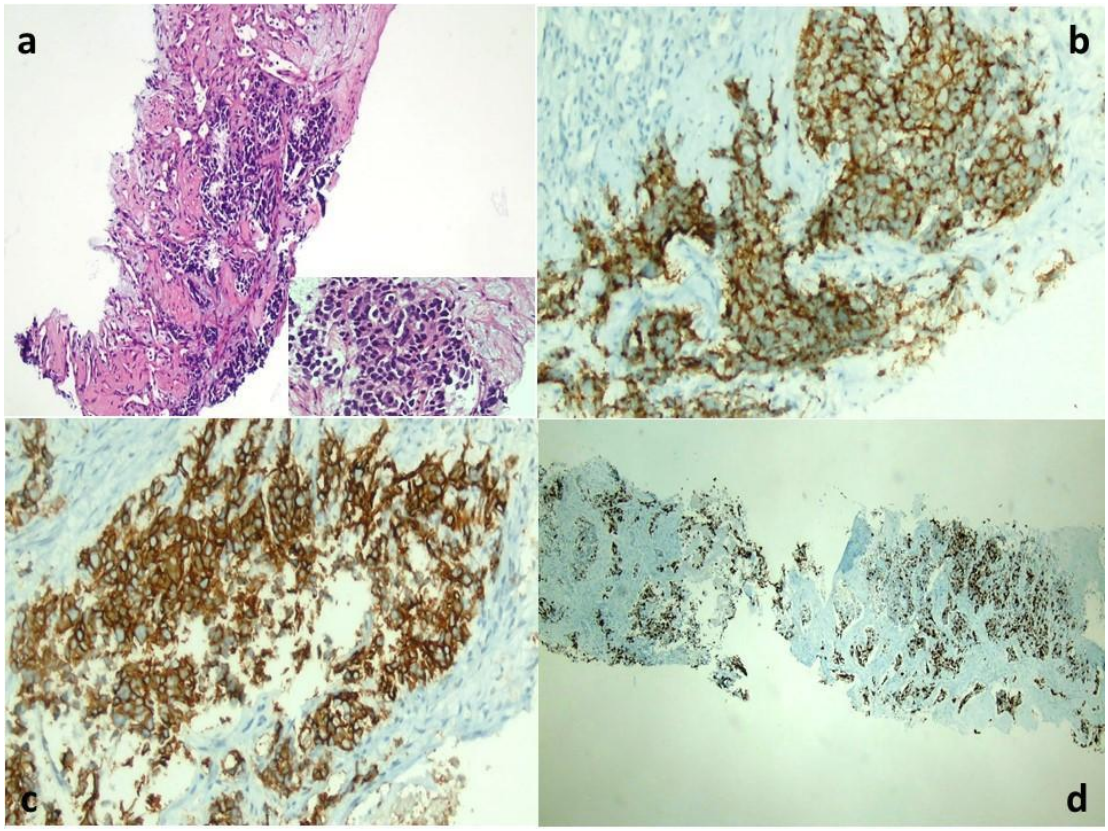

Figure 2. The tumor was composed of cells arranged in irregular cords and nest-like groups (x10), and cells with scant cytoplasm, and finely dark and granular chromatin are shown in the insert photo (x40) (a). Tumor cells exhibiting chromogranin A (b) and CD56 positivity (x20) (c), with a Ki67 proliferation index > 55% (x10) (d).

The patient was diagnosed with pancreatic small cell type neuroendocrine carcinoma. Electrodiagnostic studies were performed to examine the motor and sensory nerves of the bilateral lower extremities and the right-side upper extremity. Electromyography indicated that sensory nerve action potentials were not detected in either of the lower limbs or the right upper extremity. Motor nerve conduction study showed decreased amplitude and conduction velocity, and prolonged latency. Needle electromyography revealed reduced recruitment of the distal muscles and denervation. The patient was diagnosed with peripheral sensorimotor, dominantly axonal and particularly demiyelinating, polyneuropathy on the basis of the electromyography findings. Paraneoplastic sensory motor polyneuropathy was diagnosed since other causes of polyneuropathy had been excluded. Antineuronal antibodies (anti-Hu, -Ri, -Yo, -Ma2, -amphiphysin and -CV2) were negative. The patient was weaned from mechanical ventilation and transferred to the inpatient clinic. Palliative therapy was considered due to the patient's poor performance status, but he died one month later.

DISCUSSION

PNSs include a diverse group of disorders affecting any part of the nervous system. Although many types of tumor are reported to be associated with PNSs, lung, ovarian and breast cancers are the most commonly encountered forms in previous studies (6-9). The symptoms of PNSs precede the tumor symptoms in the majority of patients, ranging from 68% to 85% (6-8). Tumor metastasis at the time of diagnosis occurs in 21% of patients with malignancy (6). A workup for paraneoplastic etiology is therefore recommended in patients in whom other causes of neuropathy have been eliminated. Multimodality imaging including CT, MRI, ultrasonography, and endoscopy may be required to diagnose a tumor. Fluorodeoxyglucose positron emission tomography scanning is even required to detect an occult malignancy which is not observed with conventional imaging (7).

The presence of antineuronal antibodies in both the diagnosis of PNSs and for directing the investigation of underlying malignancy is well established in a wide range of patients, between 28% and 77%, and small cell lung cancer (SCLC), thymoma, ovarian cancer, melanoma and breast cancer are generally shown to be associated with these antibodies (2,7,9). Although there are many types of antibody, the best characterized antineuronal antibodies are anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma2, and anti-amphiphysin (2). However, the absence of these antibodies does not exclude a paraneoplastic syndrome (9). PNSs can present clinically as acute, subacute or chronic, and may progress, if not treated, concluding in high functional disability (7). The prognosis depends on tumor treatments (surgery, radiotherapy, and chemotherapy) which stabilize or improve the neurological symptoms, and tumors remain the primary cause of death in these patients (6,7). Early diagnosis, mRS <3, and absence of metastasis are good prognostic factors (6). In the present case, a sensorimotor axonal polyneuropathy associated with an identified metastatic cancer was diagnosed and other causes of polyneuropathy were excluded. The patient's symptoms were progressive, resulting in a mRS of 5.

Gastropancreatic NECs are high-grade (poorly differentiated) carcinomas, the counterparts of SCLC or large-cell neuroendocrine carcinomas of the lung with a high proliferative index (Ki-67 >20%), and thus more aggressive and fatal (4,5,10). They are histologically classified as small or large cell cancers, small cell cases having a poorer prognosis than large cell cases (10). The presence of necrotic areas in the tumor is a sign of a rapidly growing cancer and aggressive behavior. Lymph node involvement, diffuse liver metastasis, bone metastasis, tumor histology (small cell), poor performance status, and a high proliferative index are the most important poor prognostic factors in these patients (10-12). A large retrospective study by Sorbye et al. showed that patients with Ki-67 ≥55% had poorer prognosis than those with Ki-67 <55% (12). Median survival was 38 months for patients with localized disease, 16 months for patients with regional disease, and five months for patients with distant disease (5). A study including only pancreatic NECs reported median survival of 9.1 months, with a one-year survival rate of 34% (11). Unfortunately, median survival is only one month without chemotherapy in patients with advanced gastropancreatic NECs (12). Rapid referral to an oncologist is therefore of paramount importance. Therapeutic strategies are generally extrapolated from the treatment regimens for SCLC. The patient described in the present case had advanced disease with a poor functional state and high mitotic rate, was unable to receive chemotherapy, and died in one month after the cancer diagnosis.

PNSs are rare but important clinical conditions that often precede the diagnosis of cancers. Prompt recognition leads to tumor discovery at an earlier and curable stage. The investigation of antineuronal antibodies is useful in identifying these conditions, but negative test results do not exclude PNSs. As long-term outcomes are mainly dependent on tumor progression and its complications, early diagnosis and treatment of cancers are of paramount importance.

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