Paraneoplastic Necrotizing Myopathy Presenting as Severe Muscle Weakness in a Patient With Small-Cell Lung Cancer: Successful Response to Chemoradiation Therapy

Ho John Vu, MD
Dat Pham, MD
Raafat Makary, MD, PhD
Tim Nguyen, MD
Sania Shuja, MD, PhD

University of Florida, College of Medicine, Jacksonville, Florida

Introduction

Paraneoplastic syndromes (PNS) are defined as clinical syndromes caused by systemic effects of malignancy that are not due to direct physical effects of metastasis. The pathophysiology of PNS is not fully understood; it may result from antibodies against tumors that cross-react with normal tissues, causing injury, or injury induced by humoral factors secreted by tumor cells. PNS may fall into 1 of 4 categories: endocrine, neuromuscular, mucocutaneous, or hematologic. PNS in lung cancers include syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Cushing's syndrome, hypercalcemia, Lambert-Eaton myasthenic syndrome, and rarely necrotizing myopathy. Clinically obvious muscle weakness can occur in lung cancer patients; however, for the diagnosis of necrotizing myopathy (manifesting usually as symmetric and predominantly proximal muscle weakness), biopsy confirmation becomes essential. Tai and colleagues[1] studied 1,417 patients with several histologic types of lung cancers, among which 244 patients had small-cell lung cancer (SCLC) with limited-stage disease. Fourteen of these 244 patients had SIADH at presentation, and 2 of these 14 patients also had PNS manifesting clinically as muscle weakness; however, no biopsy was performed to document the underlying cause of muscle weakness. In another study by Gomm and associates,[2] muscle weakness with biopsy-proven necrotizing myopathy was reported to occur in 12 of 100 patients with lung cancers; however, there was no documentation whether any of these patients had SCLC. Levin and coauthors[3] reported biopsy-proven paraneoplastic necrotizing myopathy in 4 patients over a period of 10 years at their institution. Of these 4 patients, 1 had non–small-cell lung cancer, 1 had prostate cancer, and the remaining 2 had gastrointestinal tract cancer; none of these reported cases had SCLC. Nonetheless, muscle weakness associated with necrotizing myopathy has been reported in SCLC in rare cases at autopsy,[4] where diagnosis was established after the patient's death. We report a patient who presented with profound muscle weakness and loss of ambulation over a 3-month period, markedly increased creatine kinase (CK) levels, and necrotizing myopathy on biopsy from biceps muscle. Subsequent work-up revealed limited-stage SCLC, and chemoradiation therapy led to tumor regression and marked improvement in muscle weakness.

Address correspondence to:
Sania Shuja, MD, PhD, Department of Pathology, University of Florida, College of Medicine, Jacksonville Campus, 655 West 8th Street, Jacksonville, FL 32209; Phone: 904-244-4789; Fax: 904-244-4060; E-mail: sania.shuja@jax.ufl.edu.

Case Report

A 58-year-old man presented with complaints of 30-lb weight loss, generalized muscle aches, and progressive muscle weakness with loss of ambulation over a period of 3 months. The patient also had persistent cough. Pertinent physical examination revealed marked muscle weakness involving all extremities, making it impossible for him to stand up or walk. He did not have any skin rash. Initial laboratory tests revealed a CK level of 15,886 U/L (Figure 1A), alanine aminotransferase (ALT) of 521 U/L, aspartate aminotransferase (AST) of 494 U/L (Figure 1B), sodium of 122 mEq/L (normal range 135–141 mEq/L), and creatinine of 0.7. Computed tomography (CT) scan of the chest revealed a right hilar mass (Figure 2), and positron emission tomography/CT scan revealed increased uptake in the hilar mass (measuring 2.1 × 1.8 × 1.8 cm), which was suspicious for malignancy. On transbronchial fine needle aspiration from subcarinal lymph

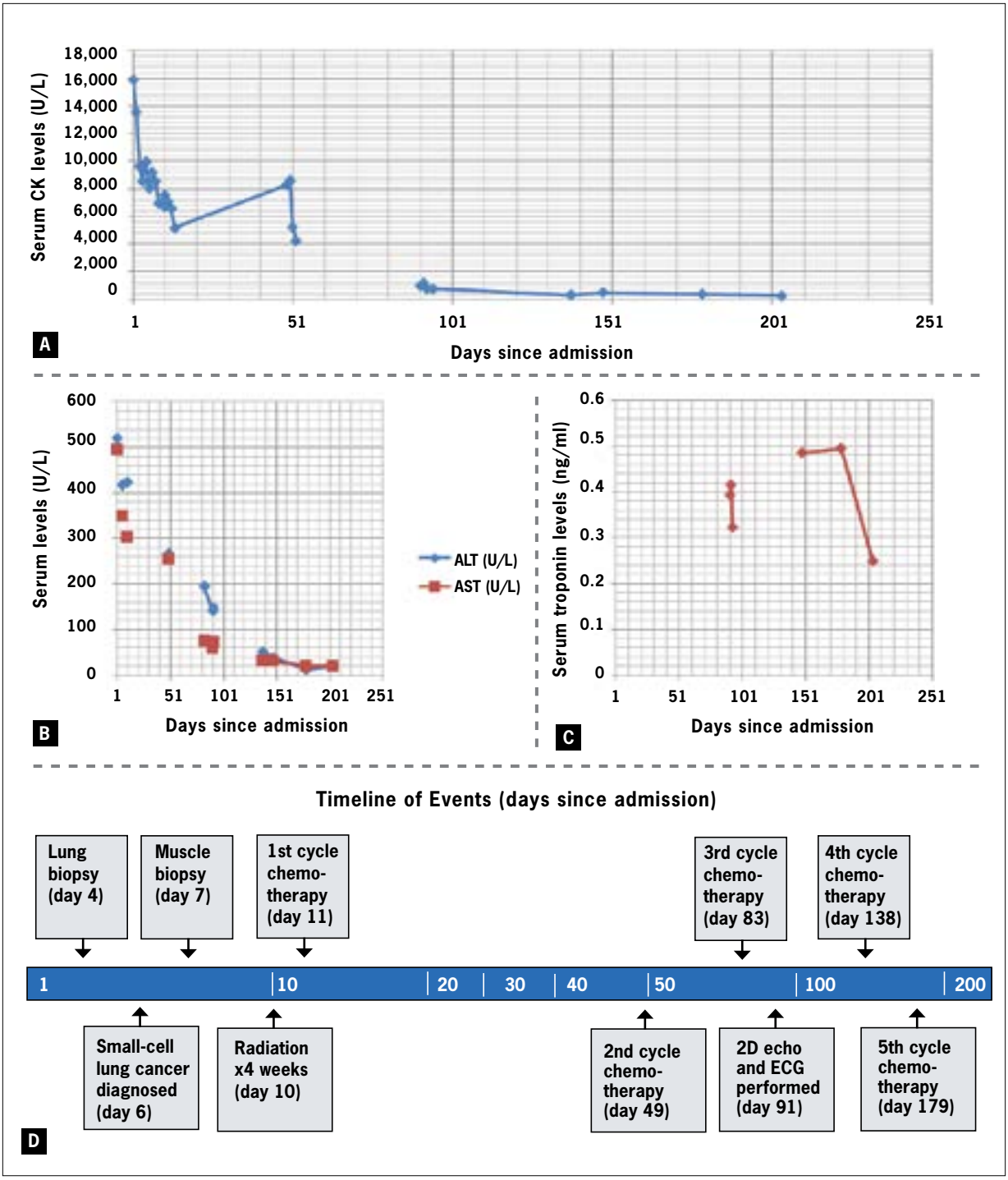

Figure 1. Serum levels of creatine kinase (CK), aspartate aminotransferase (AST), alanine transaminase (ALT), troponin-T plotted over time, and their relation to chemoradiation therapy. A) Serum CK plotted over time. The initial CK at admission was 15,886 but improved rapidly over the next few days with IV fluids. Serum CK again increased after the 1st cycle of chemotherapy but declined subsequent to the 2nd cycle and was normal after the 5th cycle of chemotherapy (209 day after initial treatment). B) Serum ALT and AST plotted over time. The ALT was initially higher than the serum AST, and had a slower decline to normal. By the 4th cycle of chemotherapy (on day 138) both ALT and AST were within the normal range (8–20 U/L). C) Serum troponin-T plotted over time. Troponin-T levels were initially obtained 91 days after hospital admission. Troponin-T levels declined after the 4th cycle of chemotherapy, although the levels did not return to normal (< 0.01) on the last test. D) Timeline of events since time of initial hospital admission to 200 days follow-up. The timeline is not measured to scale to allow all events to be represented.

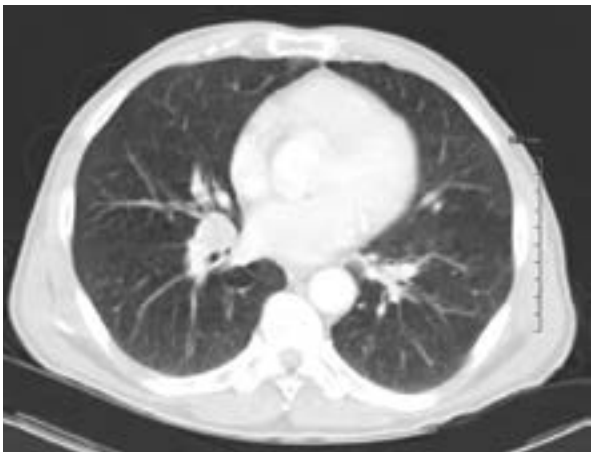

Figure 2. Computed tomography scan of the chest showing a right hilar mass.

node, a diagnosis of SCLC was established. A muscle biopsy was obtained from the right biceps muscle, and formalin fixed hematoxylin and eosin–stained sections were examined. The muscle biopsy demonstrated several individually scattered necrotic muscle fibers among relatively well-preserved, viable, and robust muscle fibers. The necrotic muscle fibers demonstrated a pink homogeneous sarcoplasm infiltrated by few to several macrophages (Figures 3A and 3B) or pale necrotic sarcoplasm infiltrated by several macrophages (Figure 3C). Muscle fiber necrosis usually involved a segment of a muscle fiber, as seen in longitudinal sections of myofibers. Macrophages infiltrated only the necrotic portion of the sarcoplasm (Figure 3D), thus myophagocytosis occurred only in the necrotic portion of the muscle fiber, with sparing of the viable portions. Few regenerative muscle fibers with basophilic sarcoplasm and enlarged nuclei were also seen. Enzyme histochemistry performed on frozen sections highlighted macrophages in red color on acid-phosphatase (Figure 3E), and brown color on nonspecific esterase stain (Figure 3F). The myopathic changes seen in the muscle biopsy, which included necrotic and degenerating muscle fibers, myophagocytosis, and presence of regenerative fibers were most consistent with the diagnosis of necrotizing myopathy. Additional studies, including acute hepatitis panel, anti-Jo antibody, HIV test, and anti-nuclear antibodies, were all negative. Magnetic resonance imaging of the brain was normal. Therapy was started on day 11 after admission (Figure 1D) and, subsequently, the patient received concurrent radiation and chemotherapy with 6 cycles of cisplatin and etoposide for limited SCLC.

Ninety days after admission, the CK level was 1,010 U/L (Figure 1A), with an MB fraction of 8%, which prompted measurement of cardiac troponin-T (Figure 1C), which was 0.416 ng/mL (normal level, <0.05 ng/mL). He did not have any cardiac symptoms, and electrocardiogram and echocardiogram were normal. There was no evidence of ischemic heart disease, and it was suggested that troponin-T elevation might be due to necrotizing myopathy or alternatively to the toxic effect of therapy on skeletal muscle. However, nonischemic cardiac injury could not be excluded.

The patient's muscle strength improved considerably, and by day 120, he was able to ambulate. On day 204,

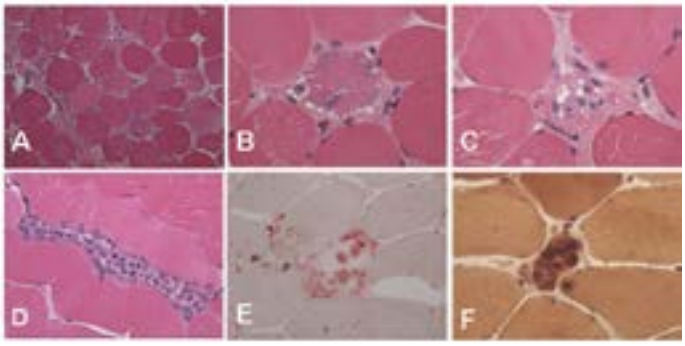

Figure 3. Muscle biopsy from right biceps muscle; hematoxylin and eosin–stained sections were obtained from formalin fixed paraffin muscle, and enzyme histochemistry was performed on frozen muscle from biopsy. A, B, and C are cross-section of muscle fibers. A) Two necrotic muscle fibers are seen among healthy well-preserved muscle fibers. B) The necrotic muscle fibers reveal pink homogenous cytoplasm; B and C) Macrophages infiltrating necrotic fibers (myophagocytosis); D) Longitudinal section of muscle fibers. A muscle fiber showing necrosis of a segment along the length of the fiber and macrophage infiltrate within the necrotic segment of the fiber. E and F) Enzyme histochemistry stains performed on frozen muscle from biopsy highlighting macrophages within the necrotic muscle fiber in red color on acid-phosphatase stain (E), and in brown color on nonspecific esterase stain (F).

liver enzymes had returned to normal, CK was slightly elevated at 277 U/L, and troponin-T was 0.2 ng/mL. PET/CT of the chest was negative, and he then received prophylactic cranial irradiation.

Discussion

Our case demonstrates that in a carefully selected group of patients with SCLC who suffer from severe muscle weakness on presentation, there is an important role for muscle biopsy in establishing early diagnosis of the underlying cause of muscle weakness. Our patient manifested severe muscle weakness and necrotizing myopathy before treatment for SCLC was started, indicating that this phenomenon was a paraneoplastic syndrome and not a secondary manifestation of toxicity due to SCLC treatment. Also, the clinical and laboratory measures of the patient's disease improved (he was able to ambulate by day 120, and CK levels dropped) with chemoradiotherapy, supporting the paraneoplastic nature of his necrotizing myopathy. Features of polymyositis/dermatomyositis were not seen, and skin rash was not reported.

The initial dramatic decline in CK from over 15,000 IU to approximately 5,000 IU was most likely due to intravenous fluids and return to optimal hydration level (Figure 1A) upon hospitalization, since this drop in CK levels occurred prior to the start of chemotherapy. The later decline in CK levels, however, correlates well with treatment response, muscle strength improvement, and weight gain.

Serum CK is considered a valuable marker in patients with skeletal muscle disease. Nonetheless, increased MB fraction may prompt a physician to measure troponin-T levels in the absence of concomitant cardiac symptoms, as reported in our case. Elevation of ALT/AST in this patient was most likely related to muscle necrosis, since elevated levels of these enzymes have been reported in patients with muscle damage occurring in polymyositis without concomitant liver disease.[5] Also, the decrease in CK levels somewhat paralleled the decrease in ALT/AST levels, with all enzymes (CK and ALT/AST levels) decreasing rapidly over the first 90 days (Figure 1A and Figure 1B). The ALT levels were always higher than the AST levels and appeared to decrease more slowly. Troponin-T levels were elevated in our patient; however, he did not have any cardiac symptoms. The latest generation of troponin-T is a highly specific cardiac marker, and it is very sensitive for myocardial necrosis. Nonetheless, it is noteworthy that elevated troponin-T levels can occur in a proportion of patients with polymyositis or dermatomyositis with no cardiac symptoms and in cases of nonischemic cardiac injury.[6,7] We believe that elevated troponin-T levels in our patient were not related to necrotizing myopathy, since troponin-T levels did not correlate well with the declining CKs (although the levels did decrease with chemotherapy). A coincidental nonischemic myocarditis could not be excluded; however, the patient had no evidence of cardiac ischemia.

In conclusion, paraneoplastic necrotizing myopathy with associated marked muscle weakness may occur as a presenting manifestation of SCLC, and treatment of the underlying malignancy can lead to dramatic improvement in muscle weakness. Although paraneoplastic necrotizing myopathy is of rare occurrence, it has been reported in other lung cancers. Thus, in carefully selected cases, muscle biopsy may be useful in evaluating the underlying cause of severe muscle weakness in patients with all types of lung cancer. Patients who present with severe muscle weakness, weight loss, elevated CK, or SIADH should be evaluated for underlying SCLC, especially if they are identified to be at increased risk (eg, heavy smokers). Serum CK, ALT, and AST appeared to be good markers of response to chemoradiation therapy in our case. However, more case studies are needed to confirm similar responses to treatment.

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Acknowledgment

This case report does not contain any patient identifiers as stated in HIPPA protocol, thus it does not require Institutional Review Board permission.

Review
Paraneoplastic Myopathy

Sakir Humayun Gultekin, MD

Oregon Health and Science University
Portland, Oregon

The Vu and colleagues describe a 58-year-old man who presented with generalized muscle pain and rapidly progressive, mostly proximal muscle weakness over 3 months with creatine kinase levels of more than 15,000 U/L.[1] Subsequently, it was discovered that he had a small-cell carcinoma in his right lung. A biopsy of his biceps revealed a necrotizing myopathy without inflammation. His muscle weakness and creatine kinase (CK) levels improved considerably after radiochemotherapy, and he was able to ambulate at 4 months after admission.

In at least two-thirds of patients with paraneoplastic neurological syndromes (PNS), an underlying neoplasm is discovered only after the neurologic syndrome develops. Therefore, a knowledge of the many clinical variations of PNS may help identify occult neoplasia and lead to more effective tumor therapy. Moreover, therapy of the underlying tumor is often the best way to manage the often disabling paraneoplastic manifestations. Tumors most commonly involved are small-cell lung cancer (SCLC), adenocarcinomas of the breast and ovary, thymoma, neuroblastoma, plasma cell tumors, and ovarian teratoma.[2]

In addition to the commonly known inflammatory myopathies (ie, dermatomyositis and polymyositis), cancer-related muscle diseases broadly include type 2 myofiber atrophy, amyloid myopathy, scleromyxedema, rippling muscle disease, myopathy with antidecorin antibodies, paraneoplastic necrotizing myopathy, and granulomatous myositis.[3] The most common paraneoplastic muscle diseases are dermatomyositis and Lambert-Eaton myasthenic syndrome.[4] Paraneoplastic necrotizing myopathy (PNM) has been classified as a "nonclassic" form of PNS.[2] Indeed, it has been very rarely described, with probably fewer than 50 cases reported since its first description in 1969.[5]

Address correspondance to:
Sakir Humayun Gultekin, MD, Oregon Health and Science University, Portland, Oregon, 3181 S.W. Sam Jackson Park Rd., Portland, Oregon 97239-3098; Phone: 503-418-1595; Fax: 503-494-2025; E-mail: gultekin@ohsu.edu.

Symptoms of PNM may mimic those of polymyositis or dermatomyositis with mostly proximal symmetrical muscle weakness that develops and rapidly progresses over several weeks with accompanying high CK levels. Muscle biopsies reveal an active necrotizing myopathy with little or no lymphoplasmacytic infiltrates. This may present a diagnostic difficulty since an identical histologic picture may occur with toxic myopathies or partially steroid-treated inflammatory myopathies, or with sampling error in otherwise typical myositis cases. In PNM, perifascicular atrophy or C5b-9 complex deposits in capillary walls typical of dermatomyositis are not identified. There is diffuse staining of the perimysial connective tissue with alkaline phosphatase. There may be rare endomysial T cells, but unlike typical cases of polymyositis, auto-aggressive T-cell invasion of intact muscle cells is not present. De novo expression of MHC-1 molecule is mostly confined to the necrotic muscle fibers in PNM, rather than the characteristic diffuse positivity encountered in typical inflammatory myopathies.[6,7]

Therapy involves the treatment of the underlying neoplasm if one is discovered. Neoplasms of the breast, gastrointestinal tract, lung, prostate, and bladder; Merkel cell carcinoma; and acute lymphoblastic leukemia have been reported.[8-10] In some patients, additional immunosuppressive therapy with high-dose steroids and intravenous immunoglobulin[11] may be effective; cetuximab may also be considered.[12] Reported outcomes are variable in PNM, ranging from complete recovery to progressive worsening of weakness.

The classic autoimmune hypothesis of paraneoplastic neurologic diseases is the de novo expression of a nonexposed nervous tissue antigen by the tumor tissue, and subsequent mounting of an immune response to that tumor antigen, resulting in a concomitant immune attack against the nervous system. Myositis autoantigen expression (Jo-1, Mi-2) is also markedly increased in regenerating muscle cells in myositis.[13] The recent discovery[14] of the presence of serum antibodies against transcriptional intermediary factor 1-gamma (anti-155/140 antibody) in a significant percentage of adult cancer-associated myositis patients will undoubtedly provide us with new insights into the relationship of cancer and muscle disease. It would be interesting to investigate if PNM patients would also have this antibody, which would hint at a continuum of pathogenetic mechanisms among these apparently different forms of cancer-associated myopathies.

This case report emphasizes the importance of a thorough search for an underlying malignancy in variable clinical presentations of myositis, and demonstrates tumor therapy as being the most effective way to control paraneoplastic disease.

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