Neurology Asia 2024; 29(3) : 849 – 852

Exploring diagnostic and therapeutic implications of subacute lower motor neuronopathy in the setting of acute lymphoblastic leukemia: A case report

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Abstract

Subacute lower motor neuronopathies (SLMN) have not been previously documented in association with acute lymphoblastic leukemia (ALL). We present a case with SLMN during the remission phase of ALL. Our patient, a young teenage male with ALL who was in remission following COTP chemotherapy, manifested weakness in the lower extremities. Following a comprehensive investigations, the patient was diagnosed with SLMN. Muscle biopsy corroborated the diagnosis, with neurogenic muscular atrophy, muscle fiber grouping and target fibers. The patient's symptom improved on two occasions following corticosteroid therapy but the symptom relapsed upon discontinuation of the medication. This case support the association of SLMN in ALL.

Keywords: Acute lymphoblastic leukemia, subacute motor neuronopathy, motor neuron disease, paraneoplastic

INTRODUCTION

Paraneoplastic neurological syndromes encompass a diverse manifestations that occur as a result of malignant tumors on the nervous system.[1-3] The spectrum of syndromes includes cerebellar degeneration, peripheral neuropathies, dermatomyositis-polymyositis, subacute motor neuron syndrome, limbic encephalitis, Eaton-Lambert syndrome, and others.[3] Although subacute motor neuronopathy has been documented as a rare paraneoplastic manifestation associated with various malignancies, such as thymoma, breast cancer, small cell lung carcinoma, renal cell carcinoma, hepatocellular carcinoma, and lymphoma[4-11], there have been no previous reports of its occurrence in acute lymphoblastic leukemia (ALL). In this report, we present a teenage male with paraneoplastic subacute lower motor neuronopathy (SLMN) with ALL.

CASE REPORT

A 16-year-old male of Chinese descent presented to the Hematology Department of the Second Affiliated Hospital of Nanchang University with dizziness and cutaneous hemorrhage. A diagnostic workup was conducted inclusive of a bone marrow aspiration and biopsy. The histopathological examination showed extensive and robust proliferation of the bone marrow, primarily characterized by the presence of primitive and undifferentiated lymphocytes. These lymphocytes were variable in size with a prevailing population of diminutive cells. Morphologically, these lymphocytes predominantly displayed a uniform and symmetrical configuration, commonly manifesting as round or elliptical in shape. Based on these pathologic findings, the patient was diagnosed with L1 subtype ALL. Following two cycles of chemotherapy (COTP protocol), he went into remission and was discharged from hospital.

In August of the third year following the initial diagnosis, the patient presented with bilateral lower limb weakness. At the onset, he had mild fatigue while walking, but his symptom progressed rapidly, leading to difficulties in climbing stairs within ten days. He sought medical attention at our outpatient department. His initial laboratory

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Date of Submission: 3 January 2024; Date of Acceptance: 28 April 2024
https://doi.org/10.54029/2024trm

test results showed an elevated creatine kinase (CK) of 231 U/L, lactate dehydrogenase (LDH) of 203 U/L and hydroxybutyrate dehydrogenase (HBDH) of 201 U/L. Electromyography (EMG) was performed with findings consistent with neurogenic muscle damage. The patient was treated with oral prednisone (20mg once daily), which resulted in some improvement. However, the medication was discontinued by the patient after the improvement.

In November of the same year, the patient developed deterioration in lower limb strength, so that he could not ambulate for the last one month. He was then hospitalized at the Neurology Department of the Second Affiliated Hospital of Nanchang University for further assessment and treatment. There was no significant family history. There were no complaints of recurrent hemorrhage, lumbago, myalgia, sensory alterations, ataxia, memory loss, changes in mentation, dizziness, headaches, visual disturbances, or numbness.

Upon admission, the patient was afebrile with a pulse rate of 80 beats per minute, respiratory rate of 20 breaths per minute, and blood pressure of 100/60 mmHg. Cardiac and respiratory examinations were normal. Muscle atrophy was observed in both lower limbs, particularly at the distal left thigh and calf. Motor weakness was observed in the proximal muscles of the lower limbs, graded as 3 on the MRC scale. Tendon reflexes were absent in the lower limbs and reduced in the upper limbs. Babinski sign was negative. Dysautonomia was not observed. Cranial nerve and sensory examinations were normal. Biochemical analysis showed elevated serum CK of 392 IU/L, LDH of 203 U/L and HBDH of 180 U/L. Tests for HIV, syphilis, liver function, kidney function, electrolytes, complete blood count, and thyroid function were all normal.

The results of the nerve electrophysiology examination are as follows: 1) Compound motor action potentials (CMAP) in both the tibial and common peroneal nerves were of low amplitudes, but conduction velocities and distal latencies remained normal. 2) Fibrillation potentials were observed in the examined muscles (Left Lateral Gastroc, Left Vastus medialis, right tibialis anterior muscle, left/L4 paraspinal muscles, right abductor pollicis brevis, right biceps brachii). Motor unit action potentials (MUAPs) were polyphasic, yet the recruitment pattern was normal. These suggests a diagnosis of motor neuron disease. Muscle biopsy findings included variations in muscle fiber size on HE staining, with compensatory hypertrophic fibers scattered among atrophic muscle bundles (Figure 1A). Atrophic fibers appeared small and circular (Figure 1B). NADH-TR staining indicated the presence of a type II muscle fiber group (Figure 2A) and a significant number of target fibers (Figure 2B), suggesting nerve regeneration and innervation of atrophied muscle fibers.

Following an exhaustive investigation into alternative causes of lower motor neuron syndrome, a diagnosis of paraneoplastic SLMN was made. During the patient's hospitalization, a one-week course of intravenous dexamethasone treatment (20 mg) led to a marked improvement in lower limb weakness symptoms, enabling the patient to regain walking ability. Discharge instructions included the continuation of maintenance treatment with prednisone.

Approximately two weeks after discharge, the patient chose to pursue traditional Chinese medicine instead of the oral corticosteroids. One to two months later, there was a significant exacerbation of muscular weakness in the bilateral lower extremities, rendering the patient to be bedridden. Sadly, the patient succumbed to a leukemia relapse after more than one year. Throughout the clinical follow-up period, motor weakness in the bilateral lower extremities persisted without notable worsening of amyotrophy, while the function of the upper extremities remained relatively unaffected.

DISCUSSION

We present a case of paraneoplastic SLMN occurring during the remission phase of ALL. This case support an association between ALL and motor neuron disease, and demonstrate the therapeutic benefits of glucocorticoid treatment.

As previously documented, individuals diagnosed with paraneoplastic motor neuronopathy exhibit three distinct clinical presentations: typical amyotrophic lateral sclerosis, motor neuron syndrome as a component of paraneoplastic encephalomyelitis, and subacute motor neuronopathies.[12,13] Notably, lymphoproliferative disorders appear to be the most prevalent among patients afflicted with paraneoplastic motor neuronopathy.[8,14] Amongst solid cancers that are concomitant with this condition, breast cancer and small cell lung carcinoma emerge as the most frequently associated malignancies.[5,14-18] The spectrum of associated cancers displays significant heterogeneity. Paraneoplastic motor neuronopathy primarily manifests as progressive weakness, typically characterized by an asymmetrical

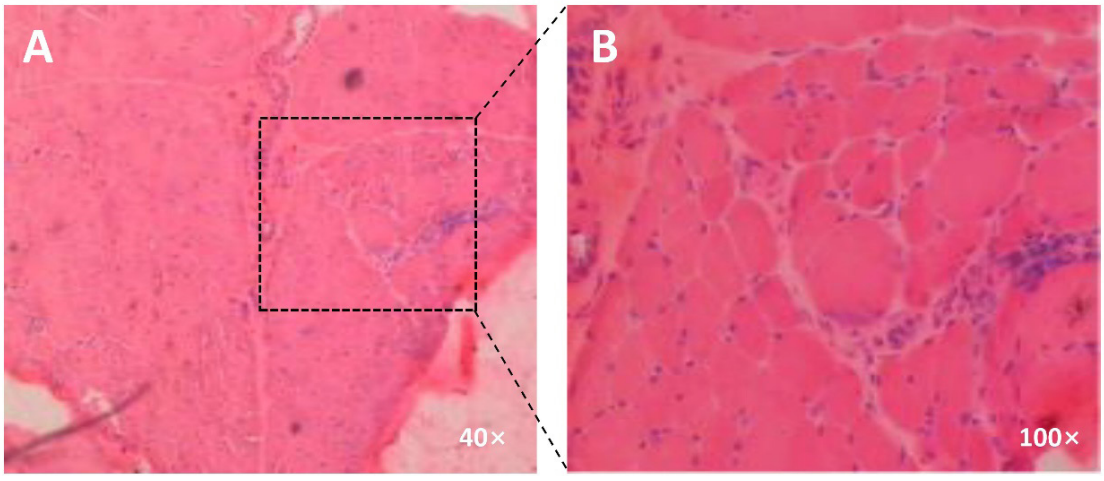

Figure 1. The pathologic changes of skeletal muscle neurogenic muscular atrophy. Shown here is the HE staining result of a biopsy from the patient's right gastrocnemius muscle. (A) The comprehensive microscopic view captures the aberrant muscle tissue structure, characterized by non-uniform muscle fiber sizes and a substantial presence of atrophied muscle fibers devoid of overt necrosis or regenerative muscle fibers. Notably, there is an absence of conspicuous inflammatory cell infiltration. (B) Within the cluster of atrophied muscle fibers, compensatory hypertrophic fibers are observed to be evenly distributed.

distribution that predominantly affects the lower extremities rather than the upper extremities. Sensory symptoms are typically absent. This syndrome can manifest at any point in time and may exhibit improvement or stabilization in parallel with the progression of the underlying cancers. The pathogenesis of paraneoplastic neurological syndromes is based on the remote effect of cancer with autoimmune mechanisms serving as the underlying pathogenic mechanism.[19]

In a case series reported by Mélé *et al*., which focused on oncological patients with motor neuron diseases, the majority of paraneoplastic motor neuron disease cases were categorized as SLMN.[20] Our current case conforms to these findings. In previous reports detailing motor neuronopathy associated with lymphoproliferative disorders, treatment of the underlying malignancy, either

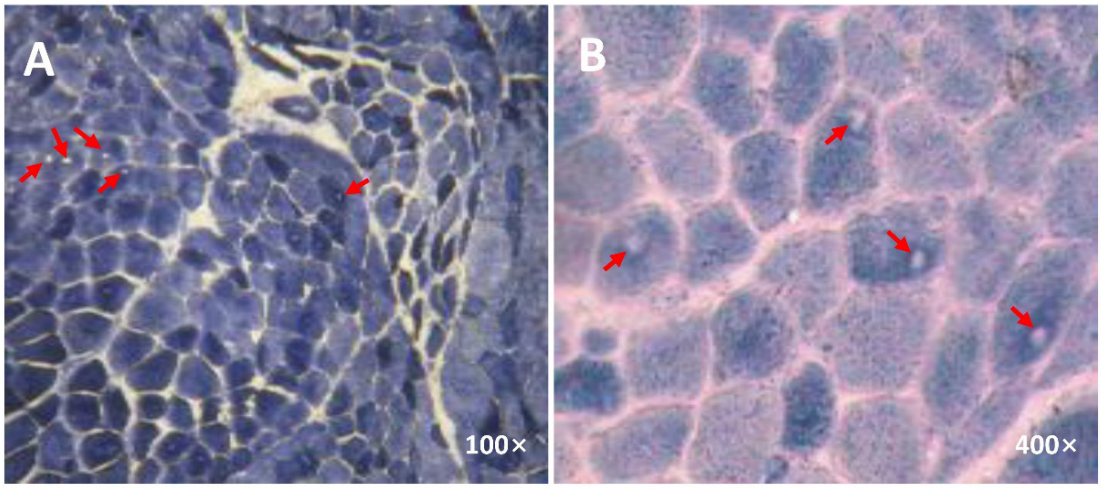

Figure 2. The NADH-TR staining of the fibrous atrophy muscle. The biopsy tissue was taken from the patient's right gastrocnemius muscle. (A) Dark blue indicated type I muscle fiber and light blue indicated type II muscle fiber. (B) Muscle fibers under high-resolution microscopic examination. The red arrows indicate specific cells. The central of the cells was not stained due to the absence of oxidase activity, the intermediate zone was deeply stained as the oxidase activity increased, the peripheral zone was stained regularly on account of the normal oxidase activity.

as monotherapy or in combination with oral corticosteroids, was associated with improvement or, at the very least, stability in the majority of cases.[8] In this patient, the administration of glucocorticoids yielded significant improvement of clinical symptoms. This outcome serves to substantiate the paraneoplastic etiology underlying the SLMN syndrome in our case. There are few documented skeletal muscle pathology in SLMN. Our patient's skeletal muscle pathology exhibited characteristic features of neurogenic muscle atrophy, prominently characterized by type II muscle fiber clustering and an abundance of target fibers, indicative of reinnervation of the atrophic muscle fibers by collateral axonal branches originating from adjacent healthy neurons.

The present study has certain limitations, chiefly stemming from the patient's decision to forego additional diagnostic investigations, including the exploration of paraneoplastic autoantibodies, cerebrospinal fluid analysis, and cranio-cervical magnetic resonance imaging scans, primarily due to financial constraints.

In conclusion, we report here an uncommon case of paraneoplastic SLMN in an ALL patient during remission, where administration of corticosteroids yielded a positive therapeutic response. To the best of our knowledge, this report is the first documented case of lower motor neuron involvement in ALL.

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