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Long-Term Nerve Conduction Changes after Successful Treatment of Poems Syndrome: Two Case Reports

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Abstract

The POEMS syndrome is a rare disorder manifesting with polyneuropathy and plasma cell dyscrasia accompanied by other multisystemic symptoms. Sensorimotor demyelinating, axonal and mixed types of polyneuropathy are the most disturbing problems of patients often leading to disability. Here we present two patients successfully treated with autologous hematopoietic stem cells transplantation. Symptoms of the POEMS syndrome entirely resolved after the treatment. Nerve conduction studies were used to follow-up patients in complete remission for few years to analyze dynamics of nerves regeneration. Despite patients clinical performance improvement, the recovery of nerve conduction was not complete. In both patients nerves of upper limbs function was restored to the greater extent than in lower limbs. Improvement or stabilization of impairment of sensory nerves conduction was followed by similar motor nerves conduction dynamic in a given limb. In addition, worsening of the electrophysiological features was observed, completing the picture of complex and subtle changes of conduction after the POEMS syndrome treatment.

Keywords: Autologous stem cell transplantation; Nerve conduction studies; POEMS; Polyneuropathy

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Introduction

POEMS syndrome is a paraneoplastic disorder related to an underlying plasma cell dyscrasia. Typically, the major manifestation is progressive sensorimotor neuropathy. Other components such as organomegaly, edema and skin changes are often overshadowed by the neuropathy. Treatment of the POEMS syndrome is not standardized. Since data from randomized clinical trials were lacking, autologous hematopoietic stem cell transplantation (auto- HSCT) became first-line treatment and yielded durable benefit and limited patient's disability [1].

Polyneuropathy, one of the mandatory diagnostic criteria of the POEMS syndrome account for increased disease burden and patients disability. Here we report two cases of patients with POEMS syndrome successfully treated with auto-HSCT. We present diagnostic challenges and focus on long-term follow-up of neuropathy symptoms and nerve function changes documented with nerve conduction studies (NCS).

Case 1

A 56-years-old man has been admitted to hospital with suspected polycythemia vera. Earlier he had a stroke with right-sided hemiparesis, which also caused multifocal vasogenic injury of the central nervous system (CNS). Imaging of the head showed numerous osteoscrelotic lesions in bones of the skull. The neoplastic disease with bone metastasis without primary focus was diagnosed. One year later patient complained about the type of gloves and stockings symptoms of peripheral sensory neuropathy and visual field limitation. Ophthalmologic examination revealed concentric visual field limitation associated with multifocal, vascular damage to CNS and bilateral optic discs edema. The physical analysis revealed vasomotor peripheral cyanosis intensified at the upright posture. High resolution computed tomography revealedosteoscrelotic lesions of ribs, pulmonary nodules and emphysema. Levels of tumor markers (CEA, AFP, Ca19.9, Ca125, PSA) were normal, and the monoclonal protein was absent, also during subsequent checks. The bone marrow showed plasma cell infiltration of 10%. Low level of vitamin B_{12} and polyglobulin presence were found. During the follow-up visits intensification of sensory polyneuropathy (3^{rd}/4^{th} degree), occurrence of hepatomegaly and splenomegaly were observed. The modified Rankin Scale (mRS) score was 3. Three years after the first hospital admission the POEMS syndrome was suspected. Results of additional examinations performed and all elements accounted for the POEMS syndrome diagnosis are listed in **Table 1.**

The patient was initially treated with dexamethasone. After two

Table 1 Diagnostic test results and POEMS syndrome diagnosis criteria [2,3] met by patients.

Parameters		Patient 1	Patient 2
Blood panel HGb RBC WBC PLT		 19.9 g/dL 6.76 x 10^{12}/ L 9.08 x 10^{9} / L 484 x10^{9} / L	 13.5 g/dL 4.49 x 10^{12}/ L 10.95 x 10^{9} / L 462 x 10^{9} / L
Bone marrow infiltration with plasma cells		16%	1%
Protein immunofixation Kappa/Lambda (plasma)		IgA λ presence 0.19	IgA κ presence 45.18
VEGF-A (normal <405 pg/mL)		3,055.6 pg/ml	290.5 pg/mL
Tumoral markers β-2-microglobulin Ki 67 proliferation index		 3.88 mg/L	 3.419 mg/L 60%
POEMS diagnosis criteria			
major	Polyneuropathy Monoclonal plasma cell proliferative disorder	+ +	+ +
other major	Castleman Disease Osteosclerotic lessions Elevated VEGF level	- + +	- + -
minor	Organomegaly Extravascular volume overload Endocrinopathy Skin changes Papilloedema Thrombocytosis&polycythemia	+ - lowered DHEA level + + both	- - hypogonadism - - thrombocythemia

cycles treatment was changed to melphalan and prednisone. The patient received 5 cycles of the treatment before the auto-HSCT. Reduction of polyneuropathy and improved quality of life were observed even before transplant. Four months after auto-HSCT patient was able to move alone and skin changes resolved. The most disturbing symptom remained were skin sensations in the lower limbs. Six monthsafter transplantation remission of disease was confirmed by lack of monoclonal protein in serum and urine and decrease of the VEGF-A concentration into the normal range (below 400 pg/ml).

Nine months after auto-HSCT, NCS showed damage of the arms nerves, and significant dysfunction of the right leg nerves with prolonged distal motor latencies conduction velocity reduction of the compound motor action potential amplitude. There was no response of the extensor digitorum brevis (EDB) muscle following left peroneal nerve stimulation and bilateral demyelination damage to the sural sensory nerves. At long-termfollow-up, the conduction in arms motor and sensory nerves gradually improved and became normal. Mixed axonal and demyelinating damage in the right peronal nerve did not improve,maintaining low amplitude and conduction velocity. Lack of response in the left motor peronal and sural sensory nerves did not change during 4.5 years of follow-up. The patient was moving independently (mRS=1).

Case 2

A 58-years-old man was admitted to the emergency department with the paraparesis. During the last 3 months, he was complaining muscles weakness and had very recent history of fall. At physical examination, paraparesis, lack of knee and ankle jerk, bilateral positive Babinski`s sign were present. mRS score was 5. Imaging studies showed osteoscrelotic destruction: fracture of diaphysis TH8 and L1, fractures of the right humerus and L1 with the presence of pathological mass surrounding it and swelling of the spinal canal. Multiple minor osteoscrelotic changes were present. Histopathological examination of a biopsy of tumor located in the area of L1 detected atypical monoclonal plasma cells with high Ki 67 proliferation rate (60%). Results of subsequent examinations performed in the hematology clinic which led to diagnosis of the POEMS syndrome are summarized in Table 1. It is worth to mention that presence of kappa chain which is a rare M-protein type in POEMS.

NCS performed at diagnosis indicated the left median motor nerve and bilateral peroneal motor nerves mixed dysfunctions (axonal and demyelinating damages), and demyelinating sensory neuropathy of sural nerves.

Vincristine, adriamycin, dexamethasone were used as induction therapy together with erythropoietin analogs and pamidronate. Improvement of patient`s performance status decreased edema of right arm and restoration of mobility of legs were observed. Stem cells were collected after 4 months of therapy. Then, the patient underwent radiotherapy in the area of Th10-L3 and was treated melphalan and prednisolone. After 7 cycles of MP monoclonal protein was not present and β-microglobulin level normalized. Fourteen months after diagnosis successful auto-HCST was performed.

Six months after transplantation, the patient moved independently using a cane (mRS=2). At 12 months after auto-

HSCT NCS showed a complete block of conduction in the right peroneal nerve, which improved in the long-term follow-up. Three years after auto-HSCT conduction in the right and left peroneal nerves improved, however,still remained largely impaired. Axonal damage of the left sensory sural nerve developed during the observation and the left leg was more impaired compared to right.

Discussion

POEMS syndrome diagnosis requires the presence of polyneuropathy and plasma cell proliferative disorder with one of three other major and one of six minor criteria (Table 1) [2,3]. Several symptoms of the disease can be absent at its onset, including mandatory ones. Due to rarity and complex, non-complete manifestation, POEMS syndrome is frequently misdiagnosed and median time from onset to diagnosis was reported to range from 12 to 18 months [3]. Prompt diagnosis is required to limit harmfulness of symptoms. Patient in the case 1 serves as an example of slowly developing disease which diagnosis took 3 years and manifested almost with all diagnostic criteria and the second patient as an example of severe onset.

Polyneuropathy in the POEMS syndrome starts with distant sensory disturbances, often accompanied by painful paresthesia of ascending character [4]. Movement symptoms which can sometimes prevail in the clinical picture as it was described in the second case. Polyneuropathy usually starts in the lower extremities with progressive proximal extension. The cranial nerves are not occupied. In the case 1 the optic field limitation was a result of subperineurial edema. POEMS syndrome was previously reported as the unusual reason for the optic disc swelling [5,6]. In the POEMS syndrome polyneuropathy demonstrates by axonal degeneration (low amplitudes) and/or uniform demyelination (low conduction velocities and increased latency) as well as mixed damages [7]. There is no correlation between the duration of the disease before auto-HSCT and the severity of the neuropathy or the response to treatment [1].

Potentially effective treatments for POEMS syndrome that have been evaluated include chemotherapy, irradiation, corticosteroids, thalidomide or lenalidomide, and blood stem cell transplantation [8]. The treatment-of-choice option is auto-HSCT [1]. Its primary goal is to achieve remission of both the hematologic and systemic manifestations. In two described cases, the treatment lead to remission of plasma cell proliferation associated with marked improvement in the patients' performance status, neurologic symptoms and other manifestations of the syndrome. The use of auto-HSCT reduced the symptoms of polyneuropathy what was observed about 1 year after transplant and improved in long-term follow-up. The fact that polyneuropathy symptoms persist longer than hematological and other systemic symptoms was confirmed previously [1]. Both axonal repair and remyelination contribute to restoration of nerve function. Both require time. It should be noted that NCS-monitored improvement concerned mainly the upper limbs in both patients when neuropathy in the lower limbs remained stable, got worse or not significantly improved despite long-term rehabilitation process. Motor conduction changes in described patients were followed by sensory changes in respective limbs. Nerves regeneration was not complete. However, the clinical neurologic outcome did not correlate with NCS outcome showing nerve damages. Despite sensimotor conduction impairment in legs both patients were moving independently, or with minimal support.

Conduction blocks (failure of action potential propagation along a structurally intact axon) are rare in POEMS syndrome [9,10] however were observed in both cases described. Predictive value of conduction block occurrence for nerve regeneration in the POEMS syndrome needs to be explained.

Conclusion

Auto-HSCT is considered as the first-line treatment for the POEMS syndrome for fit patients (evidence level IV) [1]. It allowed to achieve neurological remission in all cases summarized by Li and Zhou [3]. Nerves regeneration is a time taking processand NCS would provide independent, objective evidence about treatment outcome of the POEMS syndrome. In described cases, we could observe different patterns of nerve function changes in the long-time follow-up. It including complete conduction recovery, persistent impairment and worsening after the disease remission. Polyneuropathy monitored by NCS did not completely correlate to the physical performance of patients which can be significantly improved after treatment despite underlying disturbed or blocked nerve conduction.

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