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Peripheral Neuropathy as a Hypereosinophilic Syndrome and Anti-GM_1 Antibodies

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The acute peripheral neuropathy as one of hypereosinophilic syndrome is known to be a rare disorder. The authors experienced a dramatic case with acute peripheral neuropathy, hypereosinophilia in peripheral blood, and the positive anti-GM_1 antibodies. The serum protein electrophoresis showed a diffusely increased gamma-globulin region and the polyclonal gammopathy was found by the immunoelectropheresis. There was no evidence of inflammatory myopathy in vastus lateralis muscle. The sural nerve biopsy was compatible with vascular neuropathy, as there were a few myelin digestion chambers, mild perineuronal fibrosis, and perivascular lymphoplasmocytic infiltration with focal organizing thrombosis. The clinical response to prednisone therapy was excellent.

Key Words: *Peripheral neuropathy, hypereosinophilic syndrome, anti-GM, antibody*

INTRODUCTION

There has been noted many causes of eosinophilia, such as allergies, drug reactions, parasitic infestations. This myeloprolifestive features may cause the dysfunction of diverse tissues, including the heart, lung, skin, gastrointestinal tract, central nervous system, muscle and peripheral nerves. There could be a multisystemic involvements with hypereosinophilia, so that a new disease entity, "Eosinophilia-myalgia syndrome (EMS)", was recently introduced in which there were typical neuromuscular involvements by close association with the ingestion of L-tryptophan (Centers for Disease Control, 1989; Kibourne et al, 1990).

The peripheral neuropathy is rare in the hypereosinophilic syndrome, but their clinical, histopathological characteristics were well defined. Clinically mononeuropathy multiplex, distal symmetrical motor or sensory polyneuropathies, and radiculopathy have been reported (Dorfman et al, 1983; Grisold and Jellinger, 1985; Weaver et al, 1988). The histopathological findings in those cases have typically shown the axonal degeneration, perivascular mononuclear cell infiltration, and epineural infiltration (Dorfman et al, 1983; Weaver et al, 1988). However there were several reports saying that they were compatible with marked demyelinations as the initial pathologic events (Grisold and Jellinger, 1985).

The authors present a case who typically showed the combined involvements of muscles and peripheral nerves associated with persistent, marked eosinophilia. Interestingly the anti-GM_1 antibody titer was found to be high by the high performance thin-layer chromatography (HPTLC) and enzyme-linked immunosorbent assay (ELISA). In view of the vague pathogenetic mechanism of peripheral neuropathy in hypereosinophilia, the authors would like to suggest the role of anti-GM_1 antibody for the possible pathogenesis of peripheral nerve involvement.

CASE REPORT

A 43-year-old business man was admitted to the Department of Neurology, Seoul National University Hospital (SNUH) for the evaluation of muscle tenderness, prickling pain in the lower extremities and facial diplegia on October 22, 1990. He had been healthy until 20 days earlier, when headache and watery diarrhea developed. Also he noted erythematous macular skin rashes on his legs with an itching sensation,

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which subsided the next day. It was said that he had eaten raw chicken liver with his friends after they had finished mowing the grass around their ancester's graves one day before. The watery diarrhea persisted in spite of conservative management for about a week. In the mean time, he had felt pain in both knee joints since the fifth day of illness.

On the tenth day of his illness, muscular cramping pain developed in both legs below the knee, accompanied by a decreased temperature sensation and urinary symptoms, such as frequency and tenesmus. Two days later he felt numbness in the lower limbs and decreased sensation in the inguinal and perianal areas. Facial diplegia became prominent so that he could not close his eyes. Before being transferred to our Neurology Clinic, he was found to have diffuse hepatomegaly by liver scan, increased serum protein, and an increased number of eosinophil in peripheral blood.

At the time of admission, physical examination showed no remarkable findings apart from an acutely ill-looking appearance. On neurologic examination, facial diplegia was marked (fig. 1), but speech and swallowing were tolerable.

General muscle tone was fine. He had a mild weakness in both lower legs (MRC: grade IV). Deep tendon reflexes were slightly decreased in the upper extremities and markedly decreased or absent in the lower extremities symmetrically. Plantar reflexes were flexor.

Pain and temperature sensation were slightly

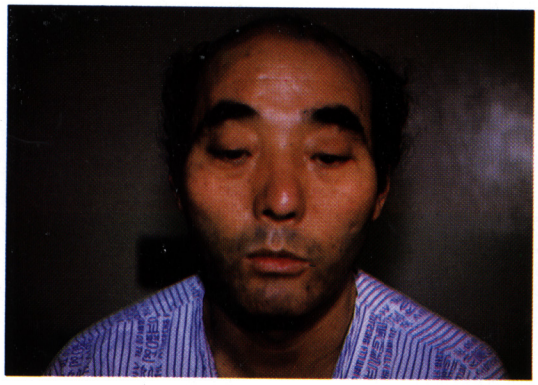

Fig. 1. The patient with acute peripheral neuropathy with hypereosinophilia, showing prominent facial diplegia. There were shallow nasolabial folds, incomplete eyeclosure and forehead wrinkling.

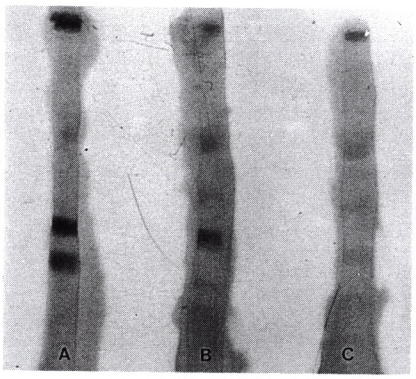

Fig. 2. The positive reaction by the patient's serum in the thin layer chromatography. (A) Positive control reacted with SGPG (3-sulfated glucuronyl paragloboside) and SGLPG (3-sulfated glucuronyl lactosaminyl paragloboside). (B) Patient's serum revealed the strong band at the same level of SGPG. (C) normal control.

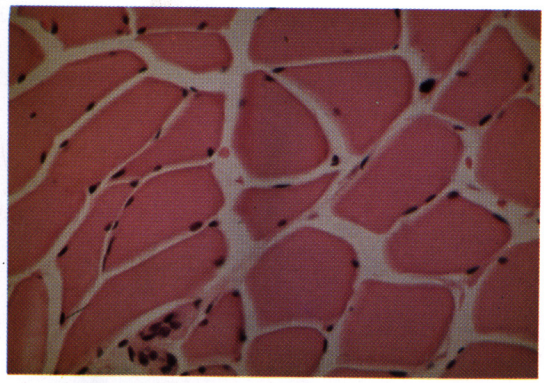

Fig. 3. A biopsy specimen of patient's vastus lateralis muscle shows a small angulated muscle fiber. But the specimen does not show any evidence of inflammatory myopathy. (H-E, ×40)

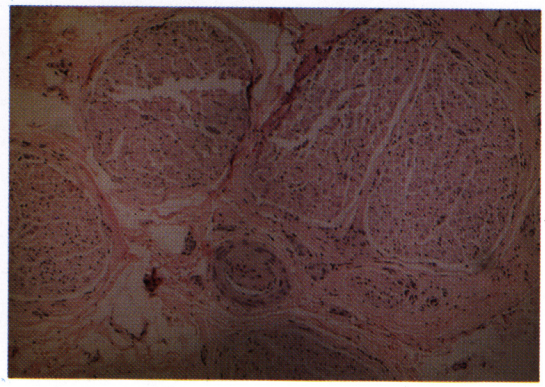

Fig. 4. Left sural nerve biopsy shows mild perineuronal fibrosis, perivascular lymphoplasmocytic infiltration. Inflammatory cells infiltrate the walls of small vessels in the epineurium with focal organizing thrombosis. (H-E, ×400).

decreased in both lower legs. Position, vibration sensory functions were good. The patient also complained of muscular pain or tenderness in the lower legs, especially below the knees.

Laboratory tests at SNUH were as follows. Urinalysis was within normal limits. Hematocrit was 40.3%, and the white blood cell count was 28,000 per mm^3, with 23% neutrophil, 8% lymphocyte and 62% eosinophil. Total platelet count was 324,000 per mm^3 and the erythrocyte sedimentation rate was 3.3mm/hour. Serum GOT was 28 U/l, the GPT 55 U/l, the CPK 137 U/l and LDH 241 U/l. ASO was negative, but the HBsAg, HSsAb, RA factor, VDRL, cryoglobulin and FANA were positive.

The brain MRI was not remarkable. Serum protein electrophoresis showed a diffusely increased r-globulin region and polyclonal gammopathy was found by serum immunoelectrophoresis. The IgE level was increased above 8000 ng/ml. The serological tests for *Borrelia burgdorferi* were negative in CSF and serum. An intense immunostaining with ganglioside was found by the HPTLC (fig. 2). And the anti-GM_1 antibody level was quantitated to be 800/1600 by the ELISA (Sadiq et al, 1990).

The CSF examination was done on the fifteenth day of his illness. The protein was increased up to 508 mg% and the cell count was 23 per mm^3, with 19 lymphocyte. The next CSF study was not remarkable except for mildly elevated serum protein levels of 178 mg%. Bone marrow biopsy was not available because of the patient's poor cooperation.

The electrodiagnositic work-up was performed two weeks after the inital sensory manifestations. There were prolonged F-wave latencies in the left median, ulnar, posterior tibial, and both peroneal nerves, increased terminal latencies in the left median, ulnar nerves, and mildly decreased nerve conduction velocity in the left median nerve, which were compatible with mild peripheral polyneuropathy. A blink test also showed moderate facial neuropathy, more marked on the left side (table 1). There were no electrophysiological evidences of denervation process in tested muscles, except for a few fibrillations in frontal muscle. Muscle biopsy in the vastus lateralis revealed no evidence of inflammatory myopathy but some angulated nerve fibers were found (fig. 3). The sural nerve biopsy showed the finding compatible with vascular neuropathy, because there were a few myelin digestion chambers, mild perineuronal fibrosis, and perivascular lymphoplasmocytic infiltration with focal organizing thrombosis (fig. 4).

We started prednisone 20mg per day after we had done those basic studies under the impression of active peripheral neuropathy, probably associated with hypereosinophilia. Muscular tenderness was relieved with several doses of prednisone. He began to feel a mild improvement of the facial diplegia so that he could wrinkle his forehead after the ninth prednisone therapy.

Table 1. Summaries of Electrophysiologic Studies

	10 days		5 months	
	Left	Right	Left	Right
Posterior tibial nerve				
Terminal latency (msec)	4.3	4.4	4.4	4.5
Motor NCV (m/sec)	41.0	43.0	40.8	44.0
CMAP amplitude (mV)	14.0	14.0	14.0	14.0
F-wave latency (msec)	50.0	49.0	50.0	49.6
H-reflex (msec)	NP	NP	—	—
Peroneal nerve				
Terminal latency (msec)	5.0	4.5	4.4	4.4
Motor NCV (msec)	45.0	44.0	45.3	43.6
CMAP amplitude (mV)	8.0	10.0	10.0	12.0
F-wave latency (msec)	54.0	52.0	50.4	50.0
Sural nerve				
Sensory NCV (msec)	37.5	36.8	—	35.8
Blink test				
R1 latency (msec)	NP	19.2	12.8	12.0
Facial nerve stimulation test				
Terminal latency (msec)	4.8	3.1	3.5	2.0
CMAP amplitude (mV)	0.7	0.3	2.4	2.3

DISCUSSION

Hypereosinophilic syndrome is a myeloproliferative syndrome in which prolonged, marked eosinophilia (above 1500 per cubic millimeter) is associated with the involvement of diverse organs. Cardiac involvement shows the changes of Loeffler's endomyocardial disease. A thickening of the endocardium with subendocardial myocardial degeneration and infiltration by eosinophils are prominent. Gastrointestinal involvement includes abdominal pains, malabsorption syndromes. Eosinophilic infiltraions in pulmonary system may reveal interstitial infiltrates on biopsy. Nonspecific urticarial, or maculopapular rashes may occur (Churg and Strauss, 1951).

With regard to the central nervous system, clinical patterns of seizures, dementia (Kaplan et al, 1989), and

cerbral infarction (Moor et al, 1985) have been described. The pathogenetic mechanisms proposed have included ischemia on either a vasculitic (Dorfman et al, 1983), or cardioembolic basis (Moor et al, 1985), and neurotoxicity (Weaver et al, 1988).

With respect to the peripheral nervous system, though peripheral neuropathy was said to be rather uncommonly associated with eosinophilia, clinically quite a few patterns of multiple mononeuropathy, distal symmetrical motor neuropathy, distal symmetrical sensory neuropathy, and radiculopathy have been reported (Dorfman et al, 1983; Grisold and Jellinger, 1985; Weaver et al, 1988). Nerve biopsy or autopsy has shown a variety of histopathologic findings consistent with wallerian degeneration (Weaver et al, 1988), axonal degeneration (Dorfman et al, 1983), demyelination, and vasculitis (Grisold and Jellinger, 1985).

The pathogenetic mechanisms of eosinophil in peripheral neuropathy are still unclear. Eosinophil contains cytotoxic granules that release eosinophil cationic protein, partially responsible for thromboembolism, neurotoxic protein, and major basic protein (Fauci et al, 1982). Some tissue damage could be due to degranulation of eosinophilic leukocytes, which are known to contain potent cytotoxins (Sunohara et al, 1989). Alternatively, it may be caused by hypoxia-ischemia from microvessel abnormalities.

Our case showed several characteristic features of acute peripheral neuropathy mimicking Guillain-Barre syndrome (GBS) or peripheral neuropathy associated with Lyme disease. Also the other most prominent finding was the markedly increased number of eosinophils in peripheral blood, which might be closely associated with the main clinical features. Howerver the antibody to *Borrelia burgdorferi* in serum and CSF was found to be negative so that Lyme disease was ruled out. It was not easy for the authors to say that this case would be the classic GBS because hypereosinophilia is not ordinarily seen in GBS although serum IgE could be elevated (Huang, 1970).

Recently another disease entity, tentatively termed "eosinopilia-myalgia syndrome (EMS)" by the Centers for Disease Control (CDC), was introduced in 1989 in North America (Centers for Disease Control, 1989; Kilbourne et al, 1990).

The current surveillance by CDC requires fulfilment of three criterias for the diagnosis of EMS: eosinophil count > 1000 cells/mm^3, myalgias of severity sufficient to interfere with a patient's ability to pursue usual activities, and exclusion of other infections or neoplastic illnesses that might account for the first two findings (Kilbourne et al, 1990)

Our case clinically resembles EMS in view of diagnostic criterias above, but the EMS has been observed to occur mainly in patients consuming oral L-tryptophan preparations (Heiman-Patterson et al, 1990; Smith and Dyck, 1990; Swygert et al, 1990). Therefore the authors could hardly say that this case could be another type of EMS.

Overall our case was typical of acute peripheral neuropathy as one of hypereosinophilic syndrome. However, the clinical features of peripheral neuropathy showed to resemble GBS. This case deserved to be a case report, as the authors were interested in the positive anti-GM_1 antibody of this GBS-like peripheral neuropathy, associated with hypereosinophilia. There were several reports saying that the anti-GM_1 antibody titer was increased in GBS (Van den Berg et al, 1992). According to Van den Berg, four out of 22 patients with GBS had raised IgM, IgG or IgA anti-GM_1 antibody activities, and the presence of anti-GM_1 antibody may define a subgroup of patients with GBS who have a poor prognosis. As for GBS, the levels of antibodies to gangliosides in the patients appear much higher than to the myelin protein antigens. The anti-ganglioside antibodies present in high levels may be better candidates for playing a meaningful pathogenetic role in some patients with GBS. Anti-GM_1 antibodies may also occur in high titer in idiopathic sensory-motor or sensory neuropathies. In those cases, the presence of high titer anti-GM_1 antibodies and improvement of symptoms after immunosuppressive therapy, like our patient, suggest that the neuropathy may be immune-mediated (Sadiq et al, 1990; Pestronk, 1991).

In our case we do not know yet whether the anti-GM_1 antibody was closely related with the GBS-like peripheral neuropathy associated with hypereosinophilia or not. However, to our knowledge, the pathogenetic bases of peripheral neuropathy due to eosinophils have not been elucidated definitely. Therefore the authors would like to suggest that the role of this antibody for the possible pathogenetic mechanisms of the peripheral neuropathy in some patients with those hypereosinophilia.

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