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Single Case – General Neurology

Myasthenia Gravis Complicated by Eosinophilic Granulomatosis with Polyangiitis: A Case Report

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Keywords

Eosinophilic granulomatosis with polyangiitis · Mononeuropathy multiplex · Myasthenia gravis · Methylprednisolone plus therapy · Cyclosporine

Abstract

A 55-year-old woman with a history of allergic sinusitis was being administered cyclosporine for ptosis and diplopia due to myasthenia gravis since age 46 years. She developed painful dysesthesia that began in her feet and later spread to her palms, leading to difficulty in walking. Eosinophils were markedly increased in the peripheral blood. Nerve conduction studies revealed mononeuritis multiplex. Nerve biopsy showed the infiltration of eosinophils in the superior neurovasculature. Based on these findings, eosinophilic granulomatous polyangiitis was diagnosed. Methylprednisolone pulse therapy was followed by oral prednisolone. Two weeks after treatment, the patient could do normal daily activities without assistance. In patients with myasthenia gravis having a history of allergic diseases, considering EGPA as a complication and monitoring prior changes in blood data are necessary for early detection before apparent tissue damage.

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Introduction

Myasthenia gravis (MG) is the most common autoimmune neuromuscular disorder. Although it is associated with various autoimmune diseases, vasculitis is a rare complication. We herein describe a novel case of eosinophilic granulomatosis with polyangiitis (EGPA)-induced mononeuropathy multiplex in an MG patient.

Case Presentation

A 55-year-old woman had a history of allergic sinusitis but no history of asthma. She had been diagnosed with ocular MG with positive anti-acetylcholine receptors at 46 years, but thymic abnormalities, thymoma, or thymic hyperplasia were not detected on chest computed tomography. Cyclosporine 2 mg/kg/day was effective for extraocular symptoms. Therefore, thymectomy was not performed as a treatment option.

One month before hospitalization, she noticed tingling over the lateral part of her right thigh and weakness in her right foot, which progressed to her left foot. Painful dysesthesia developed in both legs. Nerve conduction velocity (NCV) study revealed reduced sensory nerve action potential in the tibial and peroneal nerves and reduced compound muscle action potential in the ulnar and peroneal nerves (Table 1). The patient soon experienced painful dysesthesia in her palms that gradually worsened. Upon admission, a neurological examination revealed moderate bilateral proximal limb muscle weakness, left ankle dorsal flexion impairment, extremity areflexia, spontaneous palm and footpad pain, and vibration sensation impairment in the feet. Laboratory examinations revealed eosinophil count above the normal upper limit for several months prior to admission. Abnormal laboratory data were as follows: eosinophil count, 11,764/μL; aspartate aminotransferase/alanine aminotransferase, 36/59 IU; immunoglobulin E (IgE), 1,314 IU/mL; rheumatoid factor, 466 IU/mL; and antineutrophil cytoplasmic antibodies, negative. The radioallergosorbent test was positive for cedar pollen (class 2) and Malassezia (class 4). Computed tomography revealed mottled ground-glass opacity in the bilateral lung lobes. Two weeks after the first NCV study, a second NCV study revealed further declines in compound muscle and sensory nerve action potentials in the abovementioned nerves as well as in an additional tibial nerve (Table 1). Left peroneal nerve axonal damage in addition to right ulnar and peroneal nerve involvement was also detected. Peripheral nerves in different areas of the extremities were affected almost simultaneously, suggesting a pattern of mononeuropathy multiplex. Sural nerve biopsy revealed eosinophil infiltration in epineurium blood vessels, fibrinoid necrosis, and ruptured internal elastic lamina (Fig. 1). Cyclosporine was discontinued to rule out drug-induced eosinophilia; however, the eosinophil count remained high even after 1 week. After respiratory function tests confirmed normal lung capacity, intravenous methylprednisolone (1,000 mg/day for 5 days) was initiated for vasculitis; this was followed by oral prednisolone 1 mg/kg/day. Subsequently, the eosinophilia resolved quickly. Oral mirogabalin was administered to relieve peripheral neuropathic pain. Her gait gradually improved, and she could perform her daily activities normally without any assistance after 2 weeks of treatment. To date, prednisolone has been reduced to 5 mg/day with no increase in eosinophils and IgE or relapse of MG symptoms.

Discussion

In this case, the patient developed hyper-eosinophilia, and initially, drug-induced eosinophilia due to cyclosporine, which can affect cytokine balance, was suspected. Although cyclosporine was discontinued, the hyper-eosinophilia did not improve. This ruled out the possibility

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Table 1. Nerve conduction studies of the patient

Motor nerve conduction studies (right)	Distal latency, ms	Amplitude, mV	Conduction velocity, m/s	F latency, ms
	first study/second study (normal value)			first study
Median nerve				
Wrist-APB	3.3/3.1 (≤4.0)	12.2/10.4 (≥8.0)	57.1/54.0 (≥49.5)	24.4 (≤31)
Antecubital fossa-APB	6.7/6.8 (≤9.6)	11.9/10.1 (≥8.6)		
Axilla-APB	8.3/8.5 (≤11.1)	11.3/10.2 (≥8.6)		
Axilla-antecubital fossa			60.0/60.0 (≥56.5)	
Ulnar nerve				
Wrist-ADM	2.3/2.4 (≤3.2)	**6.8/4.7** (≥7.4)		
Above elbow-ADM	6.1/6.3 (≤7.1)	**5.6/3.5** (≥7.2)	59.7/58.0 (≥51.0)	
Tibial nerve				
Ankle-AHB	3.4/5.0 (≤6.0)	1.3/0.02 (≥0.2)		
Popliteal fossa-AHB	10.1/12.0 (≤15.0)	1.3/0.02 (≥0.3)	48.5/41.4 (≥41.0)	
Peroneal nerve				
Ankle-EDB	3.2/3.1 (≤3.5)	**0.5/0.02** (≥10.2)		Absent (≤31)
Below fibula-EDB	10.2/10.2 (≤10.8)	**0.3/0.01** (≥10.2)	48.4/43.3 (≥42.0)	
Sensory nerve conduction studies (right)	Distal latency, ms	Amplitude, mV	Conduction velocity, m/s	
	first study/second study (normal value)			
Median nerve	2.7/2.6 (≤3.4)	48.1/29.1 (≥22.9)	56.1/57.7 (≥48.0)	
Ulnar nerve	2.3/2.0 (≤3.4)	42.5/24.2 (≥20.3)	56.0/52.3 (≥47.0)	
Tibial nerve	2.2/2.1 (≤3.0)	**11.1/4.6** (≥19.9)	48.1/49.0 (≥45.0)	
Eroneal nerve	2.3/2.2 (≤3.1)	**6.5/3.9** (≥18.5)	48.9/48.0 (≥46.0)	

APB, abductor pollicis brevis; ADM, abductor digiti minimi; AHB, abductor hallucis brevis; EDB, extensor digitorum brevis.

of cyclosporine being the suspect drug. Antibiotics, malaria pills, angiotensin conversion enzyme inhibitors, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, vitamins, and supplements reportedly cause hyper-eosinophilia [1]; however, the patient had no history of taking any of these medications.

EGPA was diagnosed based on a history of allergic rhinitis, polyneuropathy, fibrinoid degeneration, and eosinophilic infiltration in peripheral nerves and hyper-eosinophilia preceding polyneuropathies. An MG case complicated with EGPA treated by tacrolimus, which represents the same calcineurin inhibitor as cyclosporine, has been reported [2]. Notably, the patient developed EGPA despite being administered cyclosporine. There is no solid evidence that calcineurin inhibitors are effective against EGPA, and therefore, it is not surprising that 2 mg/kg/day cyclosporine could not suppress EGPA development. The response of EGPA to corticosteroid therapy was favorable in this case. Up to now, only a small dose of prednisolone has been administered; however, no sign of eosinophil rise has been observed. Moreover, diplopia, as an MG ocular symptom, has not exacerbated without cyclosporine. Early improvement has been reported with methylprednisolone pulse therapy for ocular MG [3], and we consider that the use of methylprednisolone pulse therapy for EGPA has contributed to suppress the recurrence of ocular symptoms after cyclosporine discontinuation.

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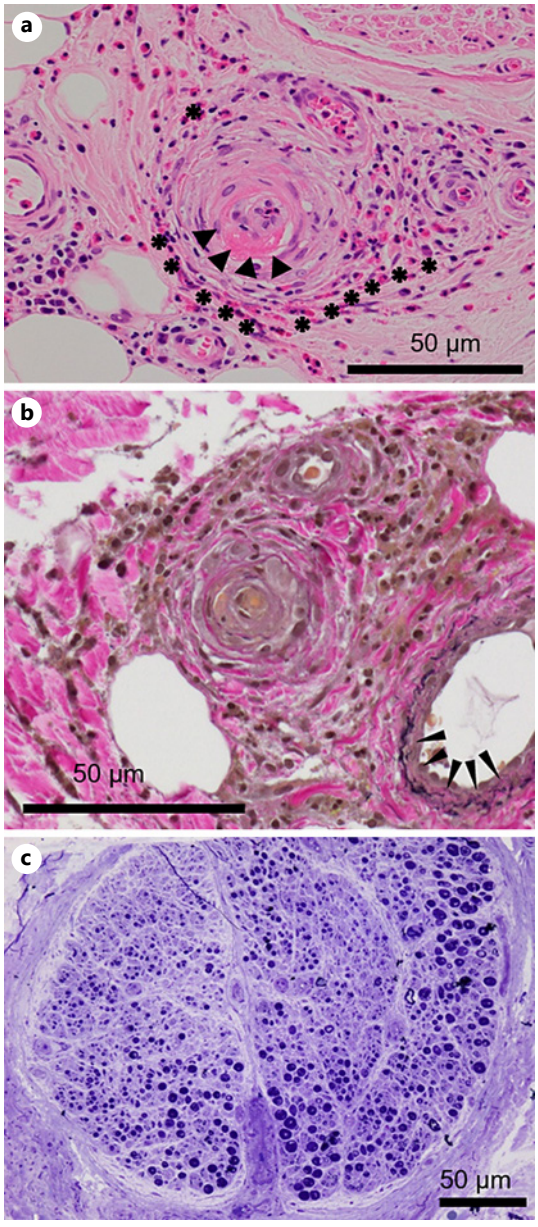

Fig. 1. Pathologic findings of a sural-nerve biopsy specimen. Transverse sections of the sural nerve. **a** Hematoxylin and eosin-stained epineurial vessel measuring 75–100 μm in diameter (×400). Fibrinoid degeneration (black arrowheads) and endothelial-cell swelling are visible. Eosinophilic infiltration and partial infiltration of plasmacytes and lymphocytes can be observed in the surrounding area (asterisks), while granuloma formation is absent. **b** Elastica van Gieson-stained slide showing tears in the internal elastic lamina (black arrowheads; ×400). **c** Semi-thin Epon-embedded toluidine blue-stained section showing nonuniform multifocal axonal degeneration (×200). Each bar in the pictures represents 50 μm.

Although MG is rarely associated with EGPA, we discuss the treatments for such cases by MG subtype which was defined by symptom distribution. In this case, methylprednisolone pulse therapy was effective for MG symptoms without an adverse effect because the patient had ocular MG. High-dose corticosteroids are typically used for the treatment of EGPA as the first-line therapy. However, high-dose corticosteroids and methylprednisolone pulse therapy should generally be avoided for the patients with generalized MG who are particularly untreated or in poor remission after immunological treatments [4]. This is because high-dose corticosteroids suppress postsynaptic acetylcholine transmission, which may exacerbate MG symptoms in these patients. For this reason, when administering moderate to high doses of corticosteroids in generalized MG with EGPA, pretreatment for MG is necessary to avoid exacerbating muscle weakness, the so-called initial worsening. Plasmapheresis should be performed before initiating corticosteroids in that case because

that can quickly improve MG symptoms and prevent corticosteroid-induced exacerbation [5, 6].

Intravenous immunoglobulin (IVIg) is effective in patients with EGPA who do not respond to corticosteroid and cyclophosphamide therapy for polyangiitis or heart failure [7, 8]. IVIg is also an effective treatment for MG as plasmapheresis [9], while IVIg monotherapy preceding corticosteroid therapy is not an established treatment for EGPA. IVIg should be used as additional medication only in corticosteroid treatment-resistant tissue damages. The immunokinetic of EGPA is T-helper type 2 cells, which play a prominent role. This results in respective clonal proliferation, activation of the humoral system, and the release of large amounts of IL-4, IL-5, and IL-13, which stimulate the humoral response of IgE-secreting B cells [10, 11]. Immunological features in MG include elevated plasma IL-17A in anti-AChR antibody-positive, early-onset, non-thymoma cases [12], increase of CD4+CXCR5+PD-1+ follicular helper T cells, which produce pathogenic autoantibodies in generalized MG [13], and decrease CD4+CD25+FoxP3+ regulatory T cells in the active phase and increase after immunologic treatment [14]. When MG and EGPA are compared, overlapped pathogenesis of the cytokine profile was few. Although several factors like occupational silica exposure, allergens, infections, vaccinations on EGPA development have been reported [15, 16], no obvious triggering episode has been identified in this case. The root cause that triggers the onset of EGPA in MG patients is still unknown. To rule out the immunological pathophysiology complications between these two diseases, further evaluation is necessary by studying more cases in future. This case suggests the need for neurologists to monitor allergic changes in blood data for early detection and therapeutic intervention for EGPA in MG patients with a history of allergic disease.

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Statement of Ethics

This study was performed in accordance with Declaration of Helsinki (1964) and its later amendments. This research protocol was waived from the need for approval under the ethics provisions of the Ethics Committee of the Toho University Ohashi Medical Center. The manuscript has been verified by the Toho University School of Medicine Paper Appropriateness Committee to ensure that the appropriate procedures have been followed for submission (Permission no. 2022-004). Written informed consent was obtained from the patient for publishing this case report and any accompanying images.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Author Contributions

Takafumi Uchi and Shingo Konno were the doctors who attended the patient and wrote the manuscript. Hideo Kihara and Mari Matsushima analyzed and interpreted the clinical data. Toshiaki Oharaseki and Kei Takahashi prepared the pathological specimen and performed pathological diagnosis. Hideki Sugimoto and Toshiki Fujioka designed and conceptualized the study, interpreted the data, and revised the manuscript.

Data Availability Statement

The data are not publicly available due to their containing information that could compromise the privacy of research patients. All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author Shingo Konno.

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