

# Complicated Acute Motor Axonal Neuropathy with Delayed Acute Respiratory Distress Syndrome and Rapidly Progressive Glomerulonephritis: a Case Report

An-Chih Chen<sup>1,6,7</sup>, Chiu-Mei Chen<sup>1,6,7</sup>, Horng-Rong Chang<sup>2,7</sup>, Kai-Jieh Yeo<sup>3,6,7</sup>, Shih-Ming Tsao<sup>4,8</sup>,  
Pei-Ching Hsiao<sup>5,6,7</sup>, Shih-Jei Tsai<sup>1,6</sup>

## Abstract-

**Purpose:** Acute motor axonal neuropathy (AMAN), a variant of Guillain Barre syndrome (GBS), is frequently induced by the antecedent infection of some atypical pathogen, such as *Campylobacter jejuni*, *Mycoplasma pneumonia* and some virus. It is generally accepted that corticosteroids and immunosuppressants are not recommended in patients with GBS including AMAN. However, if systemic autoimmune reaction developed, the principle of management might be changed.

**Case Report:** We report a young man who rapidly developed acute motor axonal neuropathy. Although plasma exchange had been given, the violent immunological reaction was unable to be controlled, prolonged leukemoid reaction and high level of autoimmunological titers, including C-reactive protein (CRP), rheumatoid factor (Rf), and antineutrophil cytoplasmic autoantibody (ANCA) persisted. Consequently, two months later, this patient developed acute respiratory distress syndrome (ARDS) and type 3 of rapidly progressive glomerulonephritis (RPGN) with rapid decline of renal function until immunosuppressants were given.

**Conclusion:** AMAN combined with the violent systemic autoimmune reaction strongly indicated an uneven disease course and implied that only standard plasmapheresis is not sufficient and corticosteroids with immunosuppressant should be added in early stage.

**Key Words:** mycoplasma pneumoniae, Guillain Barre syndrome, acute motor axonal neuropathy, rapidly progressive glomerulonephritis, antineutrophil cytoplasmic autoantibody

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From the Departments of <sup>1</sup>Neurology, <sup>2</sup>Nephrology, Divisions of <sup>3</sup>Allergy, Immunology and Rheumatology, <sup>4</sup>Infectious Disease, <sup>5</sup>Hematology and Oncology, Chung-Shan Medical University Hospital, Taichung, Taiwan; <sup>6</sup>School of Medicine, Institutes of <sup>7</sup>Medicine, <sup>8</sup>Microbiology & Immunology, Chung-Shan Medical University and Hospital, Taichung, Taiwan.  
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Correspondence to: Shih-Jei Tsai, MD, PhD. No.110, Sec.1, Jianguo N. Rd, Taichung City 40201, Taiwan.  
E-mail: cshy047@csh.org.tw

## INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute polyneuropathy consisting of different subtypes. Acute inflammatory demyelinating polyradiculoneuropathy, the classic demyelinating form of GBS, accounts for 90% of all GBS cases in the Western world. Acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN) are axonal forms of GBS that are more prevalent in Asia, South and Central America, often preceded by infection by *Campylobacter jejuni*<sup>(1)</sup>. It was also reported associated with *Mycoplasma Pneumoniae* (Mp) infection<sup>(2)</sup>.

In this report, we will present a young male who rapidly developed acute motor axonal neuropathy after a suspicious Mp infection. Although plasma exchange had been given, the violent immunological reaction was unable to be controlled, prolonged leukemoid reaction and high level of autoimmunological titers, including C-reactive protein (CRP), rheumatoid factor (Rf), and anti-neutrophil cytoplasmic autoantibody (ANCA) persisted. Consequently, two months later, this patient developed acute respiratory distress syndrome (ARDS) and type 3 of rapidly progressive glomerulonephritis (PRGN) with rapid decline of renal function until immunosuppressants were given. We would show the complicated clinical course and the difficulties with the diagnosis and management in this patient.

It is generally accepted that plasmapheresis or intravenous immunoglobulin (IVIg) therapy is the classical and standard treatment for GBS or AMAN, and corticosteroids is thought to be unnecessary and can even prolong the disease course<sup>(3)</sup>. However, in our case, the acute infection (suspicious Mp infection) might trigger systemic vasculitis with the initial presentation as AMAN. In such a condition, only plasmapheresis is insufficient.

In addition, we propose a viewpoint that the persistent leukemoid reaction and high autoimmune titers including ANCA, Rf and CRP, could be predictive for the uneven course of GBS or AMAN, much different from typical GBS, and might imply an association of subsequent systemic vasculitis, such as ANCA related disorder. Beside the plasmapheresis, early treatment with

a combination of corticosteroids and immunosuppressants is needed. This report was approved by our local ethics committee and written informed consent was obtained from our patient.

## CASE REPORT

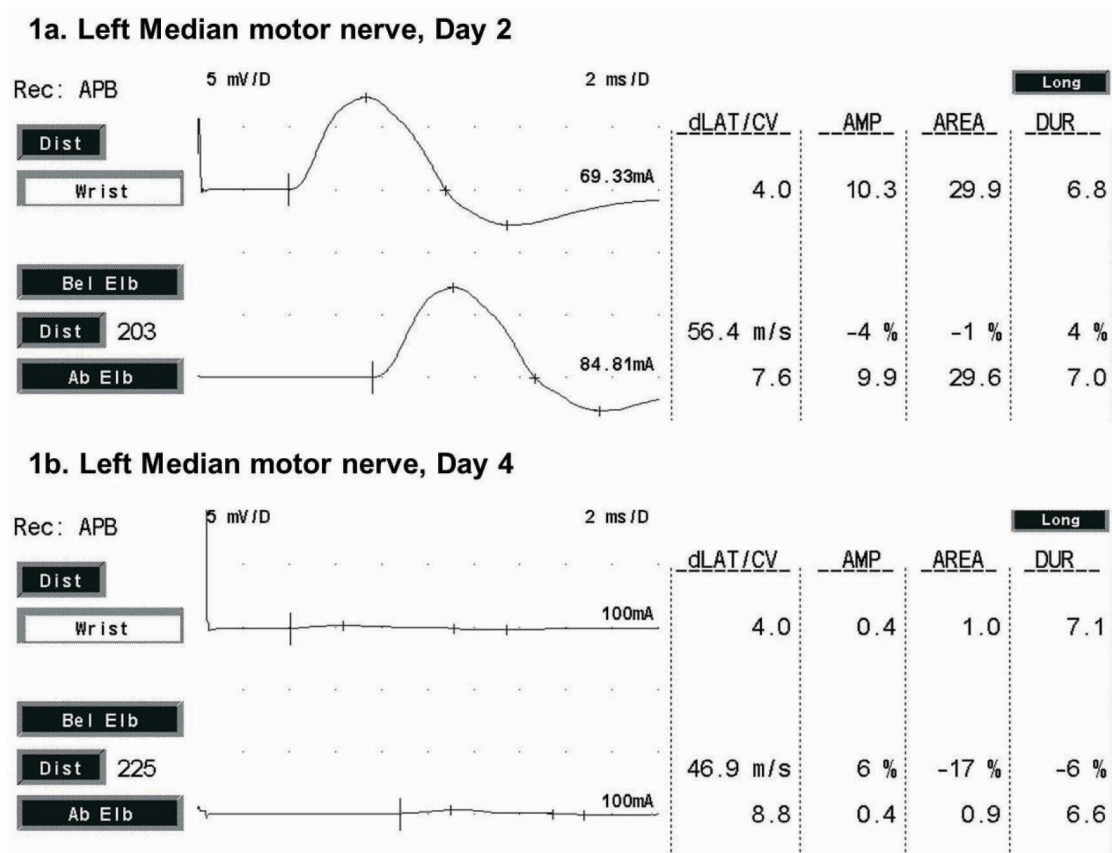
A 28-year-old man, with an unremarkable medical history, had sudden onset of bilateral foot weakness after intermittent fever and cough for one week. On admission, spiking fever up to 39 degrees Celsius, bilateral foot weakness with 4/5 muscle power and decreased bilateral ankle jerk reflexes were noted. Other physical and neurological examinations were ordinary. Initial investigations revealed neutrophil-dominant leukocytosis: total white cell count (WBC): 19950/ml with neutrophil: 81%; and elevated CRP: 14.4mg/dL. In addition, high autoimmune titers were also found, including: Rf: 1210 mg/dl; immunoglobulin (Ig)G: 2110mg/dl (normal range: 700-1600); IgA: 591mg/dl (normal range: 70-400); antinuclear antibody (ANA): 1:320X positive, speckle type; ANCA: 1:320X positive (peri-nuclear type, p-ANCA); myeloperoxidase (MPO): 76.19. Complement component 3 (C3) was normal but Complement component 4 (C4) was decreased: 7.21 mg/dL (normal range: 10-40). Normal serum creatinine level but microalbuminuria was noted in urinalysis. Further examination for the titers of connective tissue disorder, including anti-double stranded DNA antibodies and anti-extractable nuclear antigen (anti-ENA) antibodies, were all negative.

Cerebrospinal fluid (CSF) studies showed mild pleocytosis (red cell count: 20/HPF, WBC: 50/HPF: neutrophil: 20%, lymphocyte: 56%, monocyte: 24%, CSF protein: 48.3mg/dL, CSF glucose: 60mg/dL, serum glucose: 101 mg/dL, serum albumin: 2.4mg/dL). The intracranial pressure, was normal. Because the possibility of infection couldn't be excluded at that stage, empiric antibiotics was used with Ceftriaxone 2g every 12 hours. After serologic findings of mycoplasma antibody 1:320X positive and cold agglutinin 8X positive were noted, Mp infection was suspected and the antibiotic was changed to Moxifloxacin 400mg daily.

The nerve conduction velocity (NCV) studies were performed twice. The first was done on the second day after admission. It showed normal velocity but marked amplitude attenuation of compound muscle action potential (amplitude: 0.3-0.8 millivolt) in bilateral tibial and peroneal motor nerves with prolonged latency of F waves but normal motor NCVs in bilateral upper limbs. All sampled sensory NCVs in both upper and lower limbs were normal, too. The second NCV study was done on the fourth day after admission because the newly onset weakness in bilateral hands with 2/5 muscle power and more weakness of bilateral feet (muscle power: 1/5). The following NCV study showed the axonopathic change extended to bilateral median and ulnar motor nerves (Fig. 1a and 1b). Under the diagnosis of critical condition of progressive AMAN, plasma

exchange (PE) was arranged. After two times of PE (with fresh frozen plasma 30 units each time), hand weakness improved (muscle power improved to 3/5) and the fever subsided.

Despite the good results from the PE, severe allergic reaction with generalized urticaria occurred during the PE. The hydrocortisone 100~300mg was prescribed for the allergic reaction. To prevent allergic responses from allogeneic serum, PE was changed to double filtration plasmapheresis (DFPP) and corticosteroids was cancelled. Unfortunately, hand weakness (muscle power: 1/5) and fever (38.5 degrees Celsius) occurred again after DFPP for two days. We returned the treatment from DFPP to PE with corticosteroids because the effect of DFPP was debated and systemic inflammation was suspicious according the high level of the autoimmune



**Figure 1.** Nerve conductive studies: (1a) normal nerve conduction in left median motor nerve on Day 2; (1b) marked attenuation in amplitude and relative preserved conductive velocity in left median motor nerve on Day 4 (APB: abductor pollicis brevis; dLAT: distal latency; CV: conduction velocity; AMP: amplitude; DUR: duration; dist: distance; Bel Elb: bellow elbow)

titers. After PE, methylprednisolone 40mg/day was continued and tapered gradually. At last, prednisolone 2.5mg/day was kept. The neurological symptoms stopped deterioration and the fever subsided. The microalbuminuria, Rf and CRP were also improving, but leukocytosis (peak: 40830/ml) persisted. After a general survey, no infection was found. Bone marrow biopsy revealed hypercellular reaction without malignant change. The patient went home in a clinically stable condition apart from a persistent leukemoid reaction. However, he lost follow-up later.

After two months (week 11), the patient was sent to the emergency room with a spiking fever of 40 degrees Celsius and severe dyspnea. Chest radiography showed diffuse infiltration in bilateral lung fields. Because of ARDS, he received emergent intubation and mechanical ventilator support. At that time, leukocytosis (WBC: 30550/ml), anemia (Hemoglobin: 6.3mg/dL) and deterioration of renal function (serum creatinine: 2.9mg/dL) were also noted. Empiric antibiotics: Amoxicillin 500mg with clavulanic acid 100mg was prescribed every 12 hours because the possibility of septicemia could not be excluded at that stage. However, all results of infection surveys were negative including the bronchoalveolar lavage, sputum and blood culture for bacteria, fungus and virus. In addition, the autoimmune titers, including Rf (475mg/dL), CRP (11.8mg/dL) and p-ANCA (MPO: 60.19), were elevated again, but the mycoplasma titers had returned to a normal range. Prednisolone 2.5mg/day was prescribed for previous condition of active inflammation with AMAN. Fever subsided gradually then ventilator weaning smoothly one week later. The following chest radiography showed full recovery. Additionally, the skin of four limbs had ever developed annular, purpuric and macular lesions during this period. Cutaneous vasculitis was suspected. Fortunately, the skin lesion subsided gradually under the low dose of corticosteroids. Although the recovery from respiratory failure and skin lesion, renal function impairment (serum creatinine: 2.3mg/dL), proteinuria and microscopic hematuria persisted. Renal biopsy showed acute vasculitis with paucimmune necrotizing crescentic glomerulonephritis (type 3 RPGN) and secondary active tubulointerstitial nephri-

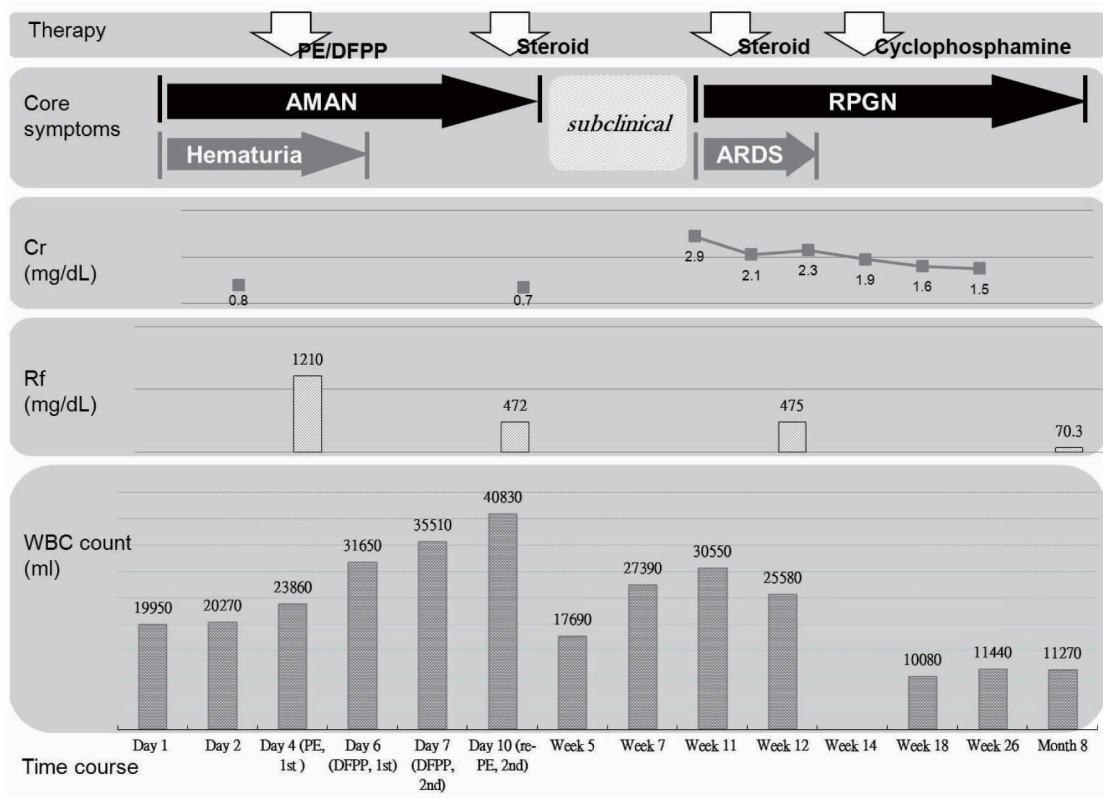
tis.

Because of a violent systemic vasculitis with organ damage, the immunosuppressant was suggested. Cyclophosphamide 50mg and prednisolone 5mg were prescribed daily. After 3 months of cyclophosphamide therapy (titrated to 100mg/day), serum creatinine lowered to 1.6mg/dL. Furthermore, the immunologic titers, including Rf and CRP, returned to normal range 8 months later. In the following 3 years, no deterioration of neuropathy was found. The weakness of bilateral hand and feet was mild improving (muscle power: 3-4/5).

## DISCUSSION

In this report, we described a young male who had severe complication after a suspicious Mp infection. AMAN developed in the initial phase, and then ARDS and RPGN subsequently developed in the second phase. Although lack of the data of needle electromyography due to patient's rejection, the diagnosis of AMAN was based on electrophysiological evidence of reduced CMAP amplitude (<80% of the lower limit of normal) but no demyelination change in two or more nerves<sup>(4)</sup>. The Mp infection was suspicious based on the clinical symptoms of upper respiratory tract infection and the detection of a high titer of mycoplasma antibody which decreased two months later. Theoretically, the direct pathogen detection of Mp, such as mycoplasma PCR test might be needed especially in cases of extrapulmonary Mp infection to rule out pseudo-positive cases. Unfortunately, this examination was unavailable in our hospital.

In this case, beside the AMAN, there seems to have an immunological violation to result in ARDS and RPGN after two months of suspicious Mp infection. High inflammatory and immunological titers, including CRP, Rf, ANCA, and marked leukemoid reaction were found since the initial stage. This was an uncommon presentation in patients of AMAN. Because severe infections and hematological problems had been excluded, the high titers might imply that the AMAN might be complicated and systemic inflammation might develop.



**Figure 2.** This figure illustrates the clinical progression of the patient with the horizontal axis representing the passage of time. The top of figure shows the clinical core symptoms and therapy. The middle of figure shows the creatinine (Cr) and rheumatoid factor (Rf) level. The bottom of figure shows the white blood cell (WBC) count. After plasma exchange (PE), double filtration plasmapheresis (DFPP) and steroids, the leukemoid reaction and the high level of Rf only decreased temporarily. In the second phase of disease, rapidly progressive glomerulonephritis (RPGN) and acute respiratory distress syndrome (ARDS) occurred. ARDS improved after steroid administration but the Cr level still deteriorated until cyclophosphamide was administered.

There are three hypothetical mechanisms for complication of the Mp infection: direct type of inflammatory cytokine production, indirect type of immune-mediated damage, or the vascular occlusion type of vasculitis or systemic hypercoagulable state<sup>(5)</sup>. However, it was worth to discuss if this patient has ANCA-associated vasculitides.

ANCA-associated vasculitides include granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, the Churg-Strauss syndrome and renal limited vasculitis. All are characterized by a focal necrotizing, pauci-immune glomerulonephritis. Nevertheless, granulomatosis with polyangiitis is primarily associated with proteinase 3 -ANCA, while microscopic polyangiitis is primarily associated with MPO-ANCA<sup>(6)</sup>. According to

these criteria, this patient was corresponded to the diagnosis of microscopic polyangiitis because of the findings of renal biopsy, positive of MPO-ANCA, and absence of granuloma formation. In short conclusion, MPO-ANCA associated AMAN with microscopic polyangiitis should be considered in this patient. The relationship between ANCA and Mp was never discussed in the reviewed articles. In our inference, Mp infection might induce AMAN and ANCA vasculitides in this patient.

In this case, the clinical course seemed to have a second phase of immunological reaction. After plasma exchange, the neurological deterioration stopped, but the elevated CRP, Rf, ANCA and WBC count only mildly decreased then increased again. It was indicated that the systemic inflammation and autoimmune reaction were

not completely controlled by PE, even with a low dose of corticosteroids. The clinical improvement in the initial stage was due to the partial immunosuppression by PE and low dose of corticosteroids, so the inflammation became subclinical. However, the disease activity increased gradually then ARDS and RPGN attacked two months later (Fig. 2). It is generally accepted that PE or IVIg therapy is the classical and standard treatment for GBS or AMAN, and corticosteroids is thought to be unnecessary and can even prolong the disease course or induce muscular weakness<sup>(3)</sup>. However, in this complicated AMAN case, only plasma exchange was insufficient. It has been proposed that plasmapheresis could only remove some autoantibodies, circulating immune complexes and dysproteins from serum<sup>(7)</sup>. The PE would not stop the progression of the immune-cascade when the systemic inflammation started. Nevertheless, corticosteroids can decrease the production of autoantibodies and can suppress the systemic immune reaction. In this case, the neurologic deterioration stopped when the corticosteroids was administered although it was used originally to suppress the allergic reaction of PE in this patient. All these findings implied that the corticosteroids needed to be added in the complicated AMAN with acute and systemic inflammation. However, the additive corticosteroids were still insufficient to suppress the violent systemic vasculitis with organ damage. This patient showed persisted leukemoid reaction and eventually developed RPGN in the second phase until the immunosuppressant was added (Fig. 2). In these view points, if we had used the sufficient doses of corticosteroids with extended duration or early combination with immunosuppressant in the first phase, the ARDS and RPGN in the second phase might not have developed.

## CONCLUSION

In conclusion, acute Mp infection might induce MPO-ANCA associated vasculitides and initially presented as a complicated AMAN. The persistent leukemoid reaction and high autoimmune titers including ANCA, Rf and CRP in patients with AMAN could be predictive for the uneven course with violent inflammation and immunological disorder, which differed from typical GBS. In such condition, careful survey to identify the ANCA-associated vasculitides is indicated. Additionally, in such a complicated case of AMAN, only plasma exchange is insufficient, corticosteroids and immunosuppressants need to be added on in the early stage.

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