Transverse myelitis associated with *Mycoplasma pneumoniae*: a report of two cases

Mielite trasversa associata a polmonite da *Mycoplasma pneumoniae*: descrizione di due casi

Aldo Parisi, Gaetano Filice
Department of Infectious and Tropical Diseases, University of Pavia, I.R.C.C.S. Policlinico San Matteo, Pavia, Italy

**INTRODUCTION**

Central Nervous System (CNS) involvement is a common extrapulmonary complication of infections due to *Mycoplasma pneumoniae*, occurring in 2-5% of cases, frequently in children, from 1-21 days after the onset of illness. The neurological manifestations of this infection include meningitis, meningoencephalitis, hemiplegia, polyradiculitis, Gullian-Barrè Syndrome, cerebellar ataxia, cerebral infarction and transverse myelitis [1].

Among these, transverse myelitis is a rare condition, reported in fewer than 10 cases until 1998 [2]. The diagnosis of the acute infection is made frequently on the clinical picture and is based on at least one of the following criteria: a fourfold rise in CF of specific antibodies, detected in two consecutive sera, a titre in IgM-ELISA of 1: 80, a single titre of cold agglutinins = 1: 128 together with a single titre of 1: 64 of CF antibodies to *M. pneumoniae* [3].

The isolation of *M. pneumoniae* from throat and other clinical specimens is usually difficult because of its cultural growth requirements. Therefore there has been considerable interest in developing rapid diagnostic tests regarding the detection of *M. pneumoniae* specific antigens or nucleotide sequences in clinical specimens: in one case of transverse myelitis, recently reported, *M. pneumoniae* was detected in LCR using nested PCR [2]. The prognosis of the disease is generally good: in a large case-study by Paine and Byers, one third of the patients had a complete recovery, one half had fair to good prognosis and only 15% had a minimal improvement of neurological symptoms [4].

In our paper, we report two cases of *M. pneumoniae* infection presenting respiratory manifestations and acute transverse myelitis following a recent episode of mononucleosis due to Epstein Barr virus (EBV). These concomitant infections probably predispose to neurological complications of mycoplasmal disease.

**CASE 1**

In May 1999, a 47-year-old male was admitted to our hospital because of meningism, bladder dysfunction, weakness and sensory deficit of the lower extremities; the tendon reflexes of the legs were normal. There was an history of fever and sore throat occurred three weeks before. The chest radiograph was normal. The Magnetic Resonance Imaging (MRI) scan of the brain was normal but the study of the spinal cord showed a segmental edema of the cervical (C4-C5) and of the lumbar tract (L4-L5). The CSF was clear, with a mononuclear pleocytosis (76 cells/dl), glucose of 42 mg/dl and a protein value of 64 mg/dl. The isoelectrofocusing of CSF revealed a blood-brain barrier damage with an increase of liquoral IgG and IgM. Gram-stained smear, bacteriological, virological and mycological cultures were negative. Microbiological serology documented the presence of antibodies against *M. pneumoniae* with a titre in IgG-ELISA of 1: 80 and a recent infection due to EBV (presence of IgG and IgM anti-VCA). The cold-agglutinin titre was 1: 128.

On the basis of these findings we made a diagnosis of *M. pneumoniae* infection and we started a combined treatment with Ciprofloxacin at doses of 400 mg/day i.v. plus Prednisone 60 mg daily i.v. for 14 days. The patient improved in his neurological status.
after 8 days from the start of therapy and a complete recovery was seen after 18 days, the final serological titre anti-micoplasma pneumoniae was 1: 160.

- **CASE 2**

On May 1999 a 31-year-old female was admitted to hospital because of headache, fever, cough and confusional state. An upper respiratory illness with sore throat, fever, lymphoadenopathy had occurred 3 weeks before. The neurological examination revealed a meningism with a Lasegue’s sign and a mild weakness of the legs; the tendon reflexes of the lower extremities were reduced. Four days later, ataxia and bladder dysfunction occurred. The chest radiograph showed diffuse interstitial infiltrates. Serological assays gave evidence of antibodies directed against VCA, EBNA and early antigen D just like a recent infection due to EBV and of antibodies against *M. pneumoniae*: this titre, tested in ELISA-IgG, was 1: 160. The cold hemoagglutinin were 1: 128. The TC scan of the brain was negative while an MRI scan of the spinal cord revealed a segmental edema of the lumbar tract. CSF analysis showed a mononuclear pleocytosis (84 cells/dl), a glucose of 33 mg/dl and a protein value of 167 mg/dl.

After a 14-day course of Ciprofloxacin at doses of 400 mg/day i.v. plus Prednisone 60 mg/day i.v. the patient improved neurologically with only mild weakness of the legs persisting.

- **DISCUSSION**

Transverse myelitis due to *M. pneumoniae* infection is a rare condition usually occurring from 1 to 21 days after the onset of respiratory illness; only in 21% of cases are no antecedent respiratory symptoms detectable [2]. The clinical picture includes weakness of the lower extremities, without complete paresis, sensory deficit, loss of bowel and bladder control; often a meningism and a mild lethargy are associated. The pathogenesis of neurological involvement is unknown and the possible mechanism proposed are a direct invasion of neural tissues or an auto-immune damage: a direct effect of *M. pneumoniae* was documented only in seven cases among 200 infected patients with CNS disease [4, 5]. More recently, in 1997, in one case of transverse myelitis *M. pneumoniae* was detected in CSF and in naso-pharyngeal aspirate by nested polymerase chain reaction [2]. Nevertheless, in view of the frequent failure to isolate *M. pneumoniae* in CSF and in brain tissue, an auto-immune pathogenesis has been proposed: auto-antibodies directed against neural tissue and circulating immune complexes were detected during the course of the infection [6-8].

Immunological alterations may probably explain the onset of extrapulmonary manifestations as transverse myelitis: the systemic spread of *M. pneumoniae* may be triggered or enhanced upon a transient depression of cell-mediated immunity [9].

*Mycoplasma* spp affect the immune system by inducing either suppression or polyclonal stimulation of B and T lymphocytes, inducing cytokines, increasing the cytotoxicity of macrophagic natural killer cells and T cells [10]. We suppose that in the 2 cases reported, a recent EBV infection, with clinical evidence of fever, sore throat and lymphoadenopathy during the 3-4 weeks before the infection with *M. pneumoniae* might probably increase the state of immunosuppression leading to a transverse myelitis: it is well known that non-EBV specific cell mediated immunity is depressed during the acute illness as measured by cutaneous anergy and decreased proliferative responses to mitogens and antigens.

EBV principally infects B-cells and later stimulates the proliferation of cytotoxic/suppressor-T lymphocytes that, together with natural killer cells, remove the transformed and “immortalized” B cells from circulation. This overactivity of T-cells leads to a transient depression of cellular immunity [10, 11]. Studies reported by Biberfeld et al. [12] demonstrate that *M. pneumoniae* is a polyclonal B lymphocyte activator and it is therefore possible that the rise in serum CF antibodies to EBV is induced by the mitogenic property of *Mycoplasma* rather than a result of recent crossinfection with the virus.

Nevertheless on the basis of the finding of specific antibodies versus EBV early antigens in one patient and of IgM anti-VCA in the other patient, we believe that a recent EBV infection was probably a predisposing factor for the extrapulmonary manifestation of *M. pneumoniae*. The prognosis of transverse myelitis in these cases is on the whole good and a complete recovery is often slow but without neurological
deficits; sporadic cases are fatal and about one-third of patients retain mild neurological dysfunction [2]. It has been reported that an appropriate treatment of transverse myelitis does not influence the prognosis; the use of corticosteroids and antibiotics remains controversial but, given the likelihood of an immunological dysfunction in transverse myelitis, corticosteroids, at high doses (60 mg/day), are recommended [6]. Antibiotic therapy is described as both beneficial and ineffective [2] but we suppose that in our two cases, early treatment including both corticosteroids and a specific antimicrobial drug (Ciprofloxacin) influenced the prognosis of the disease, leading to a complete recovery. An antibiotic regimen is probably effective when a direct invasion of \( M. pneumoniae \) in CSF is assessed, because by lowering the concentration of the bacteria, we may reduce the immunological-mediated disease. Although tetracyclines and macrolides are active against \( M. pneumoniae \) in our patients we preferred Ciprofloxacin i.v. because it provides better CSF penetration and because the concentrations obtained in the lung and in alveolar macrophages usually exceed serum concentrations [13].

**Key words:** transverse myelitis, Mycoplasma pneumoniae, EBV

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**REFERENCES**