Manifestations and Complications of *Mycoplasma pneumoniae* Disease: A Review

KLAUS LIND, M.D., Ph.D.

Head, Mycoplasma Laboratory, Statens Seruminstitut, Copenhagen, Denmark

Received January 4, 1983

Over the past 20 years the annual number of reports on extrapulmonary symptoms during *Mycoplasma* (*M.*) *pneumoniae* disease has increased. Clinical and epidemiological data indicate that symptoms from the skin and mucous membranes, from the central nervous system, from the heart, and perhaps from other organs as well are not quite uncommon manifestations of *M. pneumoniae* disease. Reports on unusual courses of the disease have also accumulated, including cases of severe respiratory symptoms, sometimes seen in patients with underlying disease or with a concomitant viral infection. Serious extrapulmonary manifestations have been common in fatal cases of *M. pneumoniae* disease.

Some observations and experimental data on these manifestations and on the possible pathogenetic mechanisms are dealt with. The conclusion is that such mechanisms are still largely unknown.

*Mycoplasma* (*M.*) *pneumoniae* is a common respiratory tract pathogen that generally produces a mild self-limited disease characterized by cough, malaise, myalgia, and headache. Lung infiltrates seen by X-ray are often accompanied by minimal or no physical findings, but a severe pneumonia may develop. Tracheobronchitis and pneumonia are the most common reasons for the patient to seek medical care. Complications are generally considered to be rare [1].

**CLINICAL MANIFESTATIONS**

Over the past 20 years an annually increasing number of unusual and severe clinical pictures of *M. pneumoniae* disease have been described, involving both the respiratory tract and other organ systems. Many of these symptoms that were described as rare complications in the 'sixties might well today achieve the rank of not quite uncommon manifestations. This achievement would depend on the proof that the non-respiratory symptoms have the same etiology as the classical respiratory symptoms of the disease. Or, there should be a significant agreement between the non-respiratory symptoms and the disease in respect of age, sex, course of illness, and epidemiology. This seems to be the case in several patients with symptoms from the skin and mucous membranes, with symptoms from the central nervous system (CNS), and with affection of the heart and perhaps other organs as well. Also, various autoimmune phenomena seem to be well-established manifestations of the disease [2-8].

**COMPLICATIONS**

Complications of *M. pneumoniae* disease such as unusual and severe courses of illness have been reported. They seem to occur predominantly in cases with involve-
ment of multiple organ systems, and the patients are generally older than those who have the classical pneumonia. Sequelae from the CNS and the heart belong to the most serious complications [8,9].

Complications may also arise within the respiratory tract, such as fulminant lobar pneumonia mimicking severe bacterial pneumonia, or such as acute diffuse alveolitis [10–12]. Abscess and cavity formation have been described, as well as large pleural effusions. Also cases of fulminant evolution into diffuse interstitial fibrosis have been reported [13–19]. Underlying diseases such as cancer, diabetes, chronic heart disease, and similar conditions may result in a complicated course of the M. pneumoniae infection [14,20,21].

Concomitant viral infections, especially such that may cause an acute immune suppression, have been reported in up to 18 percent of M. pneumoniae-diseased patients [8]. Caution should be exercised when the serodiagnosis of a viral infection is made during an M. pneumoniae infection, because of the non-specific B-cell mitogenic potency of this organism [22], a potency which it shares with some viruses. If such mixed infections do occur frequently, it may be difficult to determine whether extrapulmonary symptoms are caused by one or the other infection, or whether both may have mutually complicated the course of illness.

In the acute phase of an M. pneumoniae infection, blood lymphocytes may show a decreased response to PPD in vitro, as shown by Biberfeld and Sterner [23]. This depression of cell-mediated immunity was shown by Mogensen and co-workers [24] to be active also against other microbial antigens like Escherichia coli, Staphylococcus aureus, Bordetella pertussis, and Candida albicans. These findings may be relevant to M. pneumoniae disease complicated by other infections.

Reports on fatal cases are relatively few, but they will probably increase with the growing acknowledgement of severe, unusual, and complicated courses of the disease. To my knowledge, 20 fatal cases have been described in more or less detail in the literature [4,18,19,25–38], and additional fatal cases have been mentioned in other contexts. The overall impression is that, in addition to the pneumonia, manifestations from other organ systems contributed to the fatal outcome of the M. pneumoniae disease. In five of the 20 cases there had been CNS symptoms, in four peri- or myocarditis, and in eight coagulation disturbances. It is noteworthy that seven of the patients had received steroids. The median age of the 20 patients was 32.5 years (range 3 to 71), and the male: female ratio was 2.3:1. These cases serve to demonstrate the potential malignancy of M. pneumoniae.

EXTRAPULMONARY MANIFESTATIONS: OBSERVATIONS AND EXPERIMENTAL DATA

During the ten-year period from 1968 to 1977, we received clinical informations of 1,867 patients who had a serologically diagnosed M. pneumoniae infection. 10.8 percent had symptoms from the skin and/or mucous membranes, and 7 percent had symptoms from the CNS. The incidence of cases with these extrapulmonary symptoms in each trimester occurred in rather close parallel to the incidence of all seropositive specimens received during the period (Fig. 1). The relatively high frequency and the concurrence with the infection during major outbreaks indicate that these extrapulmonary symptoms are true manifestations of M. pneumoniae disease. The median age of all neurological patients was ten years. The last three years of this material encompassed 998 patients with M. pneumoniae infection. There were 24 cases, or 2.4 percent, of either myocarditis, pericarditis, or acute myocardial infarc-
COMPLICATIONS OF MYCOPLASMA PNEUMONIAE DISEASE

300-

200-

966 69 70 71 72 73 74 75 76 77

NUMBER OF CASES PER TRIMESTER

1 with symptoms from skin and mucous membranes
2 with symptoms from CNS

1968 69 70 71 72 73 74 75 76 77

FIG. 1. Incidence of cases with symptoms from the skin and/or mucous membranes and of cases with symptoms from the CNS among 1,867 patients with serological indication of M. pneumoniae infection (lower graph), compared with the number of anti-M. pneumoniae plus cold agglutinin positive specimens received quarterly through ten years (upper graph).

tion. Although 18 of the cases occurred in the high-incidence year 1975, the period was too short for an epidemiological evaluation [39].

Neurological complications have been described in seven of 102 patients hospitalized with a M. pneumoniae infection [4] while the corresponding Finnish figures were 4.8 percent of 560 patients [8]. In a prospective study we found among patients with acute, febrile, non-bacterial CNS affection 5 percent who had serological evidence of a current M. pneumoniae infection [7].

Cardiac symptoms during M. pneumoniae disease may be more common when looked for as described by Sands and co-workers [40] who found both light and severe cases of carditis in 8.5 percent of hospitalized M. pneumoniae-infected patients. Pönkä [9] reported that 4.5 percent of 560 patients with M. pneumoniae infection had carditis, and his epidemiological data point to an etiological role of this mycoplasma. Carré and co-workers [41] advance the hypothesis that M. pneumoniae infection may reveal or aggravate a latent coronary affection. This association was not confirmed in a recent paper by Pönkä [42].

Other non-respiratory tract symptoms seen during M. pneumoniae disease include those from the gastrointestinal tract. Mårdh and Ursing [31] have described six cases of pancreatitis following pneumonia due to this infection. Diabetes mellitus developed in two of these, and one case was fatal. In this context it should be noted that Finnish workers have questioned the specificity of CF antibodies to M.
*pneumoniae* in acute pancreatitis [43]. Hematological symptoms in *M. pneumoniae* disease are rare. Both hemolytic anemia and disturbance of coagulation mechanism have been reported. Signs of disseminated intravascular coagulation have been described, especially in fatal cases. Also arthritis is a rare complication in *M. pneumoniae* disease [1-3, 8].

**PATHOGENESIS OF EXTRAPULMONARY MANIFESTATIONS: OBSERVATIONS AND EXPERIMENTAL DATA**

The extrapulmonary manifestations of *M. pneumoniae* disease may be a result of the presence of the pathogen in the target organ or organ system. The paucity of reports on isolation of *M. pneumoniae* from skin eruptions and CNS favors the hypothesis of an indirect effect of the microorganism in most cases [44-47]. So far, however, no neurotoxin has been demonstrated for this mycoplasma. In several cases a tendency to hypercoagulation has been reported, and intravascular clotting in the CNS cannot be excluded as a pathogenic mechanism [8].

The variety of neurological clinical pictures which may be seen in *M. pneumoniae*-infected patients, both with and without respiratory tract symptoms, and the different time relation to onset of illness and to antibody development may give the impression that more than one mechanism is operating [7]. The possibility of an indirect immune mechanism was advanced when Biberfeld found complement-fixing (CF) antibodies to brain tissue antigen in patients with *M. pneumoniae* infection. However, not all patients had neurological manifestations [48]. In a prospective study of patients with neurological symptoms, we found CF antibodies to brain antigen at a high titer in three of ten patients with a current *M. pneumoniae* infection, while in 82 neurological patients without evidence of this infection no antibodies to brain were detected [7].

By investigation of sera from more than 100 patients with *M. pneumoniae* infection, we found that CF antibodies to brain tissue antigen were present mainly together with high titer CF antibodies to *M. pneumoniae*. When two matched groups of *M. pneumoniae* patients were compared, selected in twos by the same anti-*M. pneumoniae* titer, one with and one without neurological symptoms, antibodies to brain were found significantly more often among the neurological patients (Table 1) [39].

We fractionated sera by density gradient ultracentrifugation and tested the IgM and IgG classes for antibodies to brain tissue and to *M. pneumoniae*. In two of four

**TABLE 1**

Complement-Fixing Antibodies to Human Brain Tissue in Two Groups of Patients with Positive Anti-*M. pneumoniae* Test

| CNS Symptoms Present | Number of Patients | Median Age (range) | Male/Female | Patients with Respiratory Symptoms | Bronchitis or URI* | None | Antibrain Titer |
|----------------------|--------------------|--------------------|-------------|-----------------------------------|--------------------|------|----------------|
| YES                  | 49                 | 23 (1-79)          | 31/18       | 37                                | 6                  | 6    | 19*           |
| NO                   | 49                 | 23 (2-70)          | 23/26       | 42                                | 3                  | 4    | 8*            |

* *URI, upper respiratory tract infection*

*2p = 0.023*
COMPLICATIONS OF MYCOPLASMA PNEUMONIAE DISEASE

TABLE 2
Absorption of Human and Rabbit Sera with *M. Pneumoniae* and Human Brain Tissue

| Serum                                      | Absorbed with | Complement Fixation Titer of Antibodies to |
|--------------------------------------------|---------------|---------------------------------------------|
| From 24-year-old female with pneumonia     | *M. pneumoniae* | Brain 5,000                                 |
|                                            | Human brain   | *M. pneumoniae* 64                          |
|                                            | < 16          | Human brain 2,000                            |
| Pool from four rabbits given live *M. pneum.* intravenously | 0 | Brain 4,000 |
|                                            | *M. pneumoniae* | *M. pneumoniae* < 8 |
|                                            | Human brain   | Human brain 2,000                            |

patients with meningitis the anti-brain antibodies were found both in the IgM and the IgG fractions. In the other two patients antibodies to brain were found in the IgM class only. In sera from seven pneumonia patients without neurological symptoms, antibodies to brain were found exclusively in the IgM fractions. Sera from all these patients, both with and without neurological symptoms, had high titers of antibodies to *M. pneumoniae* both in the IgM and IgG fractions. Antibrain antibodies were detected between one and 14 days after onset of neurological symptoms, on the average on day 6 [39]. The results are in accordance with fractionation experiments of Biberfeld, who also looked for these antibodies in the spinal fluid of two neurological patients with negative results [2,48].

We found that absorption of patients' sera with *M. pneumoniae* antigen reduced the titer of antibodies both to the homologous antigen and to brain tissue antigen. However, absorption with brain tissue only removed antibrain antibodies but did not significantly reduce the titer of antibodies to *M. pneumoniae*. Similar results were obtained by absorption of sera from rabbits immunized with *M. pneumoniae* (Table 2) [39]. This partial cross-reaction between antigens of human brain and *M. pneumoniae* has also been shown by Biberfeld [2], and it could be further demonstrated when the antigens were used as immunogens in rabbits. As shown in Table 3, subcutaneous injections of human brain tissue with adjuvant gave rise to

TABLE 3
Antibodies in Rabbits Vaccinated with Human Brain Tissue or with *M. pneumoniae*

| Number of Rabbits | Vaccinated with | Complement Fixation GM Titer of Antibodies to |
|-------------------|-----------------|---------------------------------------------|
|                   |                 | Brain  | *M. pneumoniae* |
| 5                  | Human brain + FCA subcutaneously | 388    | < 16           |
| 2                  | Killed *M. pneum.* + FCA subcutaneously | ≤ 8    | 4,000          |
| 4                  | Live *M. pneum.* intravenously | 1,145  | ≥ 4,000        |

GM, Geometric mean
FCA, Freund's complete adjuvant
antibodies to brain but not to \textit{M. pneumoniae}, and killed mycoplasmas with adjuvant injected by the same route resulted in formation of antibodies to this antigen but not to human brain. However, when rabbits were given live \textit{M. pneumoniae} intravenously, they produced antibodies both to \textit{M. pneumoniae} and to human brain tissue. The results from giving this live vaccine may reflect the natural \textit{M. pneumoniae} infection in man; none of the four rabbits showed any neurological symptoms [39]. The pathogenic role of these antibodies is not known. This is true also of immune complexes which were demonstrated by Biberfeld and Norberg in the blood during the acute phase of the disease [49].

Another neuropathogenic activity might be one mediated by lymphocytes. When testing blood lymphocytes from patients with \textit{M. pneumoniae} infection and neurological symptoms Mogensen and Lind [50] found that responses to stimulation with \textit{M. pneumoniae} antigen \textit{in vitro} tended to be low or normal in patients who had no pleocytosis in the spinal fluid or no pulmonary infiltrates, while responses were high when either pleocytoses or a pneumonia was present. The high responses were comparable to those obtained with lymphocytes from patients with classical \textit{M. pneumoniae} pneumonia. The low lymphocyte response which corresponded to lack of lymphocyte accumulations might be due to an effect of antigen-specific suppressor T-lymphocytes.

**CONCLUDING REMARKS**

The pathogenic mechanisms of the various manifestations and complications of \textit{M. pneumoniae} disease are still largely unknown. The endeavor to unveil these mechanisms should include attempts to demonstrate the specific antigen in the target organs and tissues. It might prove profitable to investigate further the possible pathogenic role of subpopulations of lymphocytes and their products in \textit{M. pneumoniae} disease. As a basis of these investigations, the serological criteria of the diagnosis of this disease should be re-evaluated.

**REFERENCES**

1. Clyde WA Jr: Mycoplasma pneumoniae infections of man. In The Mycoplasmas. Human and Animal Mycoplasmas. Edited by JG Tully, RF Whitcomb. New York, San Francisco, London, Academic Press, 1979, Vol II, pp 275-306
2. Biberfeld G: Immunological, Epidemiological and Ultrastructural Studies of Mycoplasma pneumoniae. Thesis, Stockholm, 1971
3. Feizi T, MacLean H, Sommerville RG, et al: Studies on an epidemic of respiratory disease caused by Mycoplasma pneumoniae. Br Med J i:457–460, 1967
4. Sterner G, Biberfeld G: Central nervous system complications of Mycoplasma pneumoniae infection. Scand J Infect Dis 1:203–208, 1969
5. Foy HM, Grayston JT: Pneumonia, Mycoplasma pneumoniae. In Communicable Infectious Diseases. Edited by FH Top, PF Wehrle. St Louis, CV Mosby & Co, 1972, pp 480–494
6. Lind K: Mucocutaneous reactions during Mycoplasma pneumoniae infection. Lancet i:655, 1978
7. Lind K, Zoffman H, Larsen SO, et al: Mycoplasma pneumoniae infection associated with affection of the central nervous system. Acta Med Scand 205:325–332, 1979
8. Pönkä A: The occurrence and clinical picture of serologically verified Mycoplasma pneumoniae infections with emphasis on central nervous system, cardiac and joint manifestations. Thesis, Department of Virology, University of Helsinki, Helsinki, Finland. Ann Clin Res 11 Suppl 24:1–60, 1979
9. Pönkä A: Carditis associated with Mycoplasma Pneumoniae infection. Acta Med Scand 206:77–86, 1979
10. Stallings MW, Archer SB: Atypical Mycoplasma Pneumonia. Am J Dis Child 126:837–838, 1973
11. Cockcroft DW, Stilwell GA: Lobar pneumonia caused by Mycoplasma pneumoniae. Can Med Assoc J 124:1463–1468, 1981
12. Mlezoch F, Witek F: Miliary Mycoplasmal Pneumonia: A Report of Six Cases. Infection 4 Suppl 1:64–67, 1976
13. Kawata K, Sumino Y, Kikuchi Y, et al: Two Cases of Mycoplasmal Pneumonia with Cavity Formation. Jap J Med 17:144–147, 1978
14. Solanki DL, Berdoff RL: Severe Mycoplasma Pneumonia with Pleural Effusions in a Patient with Sickle Cell-Hemoglobin C (SC) Disease. Case Report and Review of the Literature. Am J Med 66:707–710, 1979
15. Chester A, Kane J, Garagusi V: Mycoplasma Pneumonia with Bilateral Pleural Effusions. Am Rev Respir Dis 112:451–456, 1975
16. Domenighetti G, Perret C: Mycoplasma pneumonia with fulminant evolution into diffuse interstitial fibrosis. Thorax 35:960, 1980
17. Kaufman JM, Cuvelier CA, Van der Straeten M: Mycoplasma pneumonia with fulminant evolution into diffuse interstitial fibrosis. Thorax 35:140–144, 1980
18. Reigner P, Domenighetti G, Feihl F, et al: Syndrome de détresse respiratoire aigu sur infection à mycoplasmes. Schweiz Med Wochenschr 110:221–223, 1980
19. Fraley DS, Ruben FL, Donnelly EJ: Respiratory Failure Secondary to Mycoplasma pneumoniae Infection. South Med J 72:437–440, 1979
20. Foy HM, Ochs H, Davis SD, et al: Mycoplasma pneumoniae infections in patients with immunodeficiency syndromes: Report of four cases. J Infect Dis 127:388–393, 1973
21. Ganick DJ, Wolfson J, Gilbert EF, et al: Mycoplasma Infection in the Immunosuppressed Leukemic Patient. Arch Pathol Lab Med 104:535–536, 1980
22. Biberfeld G, Arneborn P, Forsgren M, et al: Non-specific polyclonal antibody response induced by Mycoplasma pneumoniae. Tokyo 1982. Yale J Biol Med 56:639–642, 1983
23. Biberfeld G, Sterner G: Effect of Mycoplasma pneumoniae Infection on Cell-Mediated Immunity. Infection 4 Suppl 1:17–20, 1976
24. Mogensen HH, Andersen V, Lind K: Lymphocyte Transformation Studies in Mycoplasma pneumoniae Infections. Infection 4 Suppl 1:21–24, 1976
25. Meyers BR, Hirschman SZ: Fatal Infections Associated with Mycoplasma Pneumoniae: Discussion of Three Cases with Necropsy Findings. Mt Sinai J Med NY 39:258–264, 1972
26. Melkiojohn G, Eaton MD, van Herick W: A clinical report on cases of primary atypical pneumonia caused by a new virus. J Clin Invest 24:241–250, 1945
27. Maisel JC, Babbitt LH, John TJ: Fatal Mycoplasma pneumoniae infection with isolation of organisms from lung. JAMA 202:287–290, 1967
28. Schubothe H, Merz KP, Weber S, et al: Akute autoimmunhämolytische Anämie vom Kälteantikörper nach Mykoplasma-pneumonie mit tödlichem Ausgang. Acta Haematol (Basel) 44:111–123, 1970
29. Nilsson IM, Rasing A, Denneberg T, et al: Intravascular coagulation and acute renal failure in a child with mycoplasma infection. Acta Med Scand 189:359–365, 1971
30. De Vos M, Van Nimmen L, Baele G: Disseminated Intravascular Coagulation during a Fatal Mycoplasma pneumoniae Infection. Acta Haematol 52:120–125, 1974
31. Mårth P-A, Ursing B: The Occurrence of Acute Pancreatitis in Mycoplasma Pneumoniae Infection. Scand J Infect Dis 6:167–171, 1974
32. Naftalin JM, Wellisch G, Kanana Z, et al: Mycoplasma Pneumoniae Septicemia. JAMA 228:565, 1974
33. Dorff B, Lind K: Two Fatal Cases of Meningoencephalitis Associated with Mycoplasma pneumoniae Infection. Scand J Infect Dis 8:49–51, 1976
34. Halal F, Brochu P, Delage G, et al: Severe disseminated lung disease and bronchiectasis probably due to Mycoplasma pneumoniae. Can Med Assoc J 117:1055–1056, 1977
35. Oldenburger D, Carson JP, Gundlach WJ, et al: Legionnaires' disease. Association With Mycoplasma Pneumonia and Disseminated Intravascular Coagulation. JAMA 241:1269–1270, 1979
36. Koletsky RJ, Weinstein AJ: Fulminant Mycoplasma pneumoniae Infection. Report of a fatal case, and a review of the literature. Am Rev Respir Dis 122:491–496, 1980
37. Weinblatt ME, Caplan ES: Fatal Mycoplasma pneumoniae Encephalitis in an Adult. Arch Neurol 37:321, 1980
38. Sands MJ, Rosenthal R: Progressive Heart Failure and Death Associated with Mycoplasma Pneumoniae. Chest 81:763–765, 1982
39. Lind K: Unpublished
40. Sands MJ Jr, Satz JE, Turner WE Jr, et al: Pericarditis and Perimyocarditis Associated with Active Mycoplasma pneumoniae Infection. Ann Intern Med 86:544–548, 1977
41. Carré J-C, Conduoret S, Chabanon G, et al: Manifestations cardio-pulmonaires des infections par le Mycoplasma pneumoniae. Nouv Presse Méd 7:2373–2376, 1978
42. Pönkä A, Jalanko H, Pönkä T, et al: Viral and mycoplasmal antibodies in patients with myocardial infarction. Ann Clin Res 13:429–432, 1981
43. Pönkä A, Pönkä T, Sarna S, et al: Questionable specificity of lipid antigen in the Mycoplasma pneumoniae complement fixation test in patients with extrapulmonary manifestations. J Infect 3:332–338, 1981
44. Lyell A, Gordon AM, Dick HM, et al: Mycoplasmas and erythema multiforme. Lancet ii:1116–1118, 1967
45. Canton P, Clozel M, Neiman L, et al: Erythème polymorphe. Isolement de Mycoplasma pneumoniae dans les lésions cutanées. Nouv Presse Med 9:1516–1518, 1980
46. Fleischhauer P, Hüben U, Mertens H, et al: Nachweis von Mycoplasma pneumoniae im Liquor bei akuter Polyneuritis. Dtsch Med Wochenschr 97:678–682, 1972
47. Kitamoto O: Personal communication of M. pneumoniae isolated from the CSF in 5 cases of M. pneumoniae pneumonia in Japan, 1981
48. Biberfeld G: Antibodies to brain and other tissues in cases of Mycoplasma pneumoniae infection. Clin Exp Immunol 8:319–333, 1971
49. Biberfeld G, Norberg R: Circulating Immune Complexes in Mycoplasma Pneumoniae Infection. J Immunol 112:413–415, 1974
50. Mogensen HH, Lind K: In vitro stimulation of blood lymphocytes from Mycoplasma pneumoniae infected patients with pneumonia and with disorders of the central nervous system. Acta Pathol