Other Organs

YOJI SUZUYAMA, M.D., HIROMARU IWASAKI, M.D., KINICHI IZUMIKAWA, M.D., AND KOHEI HARA, M.D.

2nd Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

Received January 4, 1983

Although self-limited respiratory tract infections caused by Mycoplasma pneumoniae are well recognized in children and young adults, respiratory involvements and hepatic dysfunction may occur. The frequency and clinical features of these complications were investigated. Experimental studies with regard to bacterial superinfection were also carried out. The test animals which were first infected with Mycoplasma pneumoniae and then with Staphylococcus aureus showed more extensive bacteriological and pathological changes than those infected with Staphylococcus aureus only. Liver biopsies performed on three human patients showed hepatic dysfunction and the histological findings were diagnosed as non-specific reactive hepatitis in each case.

INTRODUCTION

Mycoplasma pneumoniae (hereafter abbreviated as M. pneumoniae) is well recognized as the causative organism of respiratory tract infections in children and young adults. In general, it has been considered that the prognosis for M. pneumoniae pneumonia is good, and there are few complications. However, organ systems other than the respiratory may be affected by M. pneumoniae infection. This infection has caused severe pulmonary complications, including pleural effusions, multilobe distribution, abscess formation, and respiratory failure [1-4]. The involvement of other organ systems, including the neurologic, gastrointestinal, cardiovascular, dermatologic, and musculoskeletal, is less well appreciated [5-8].

In adults, the incidence of such complications is generally low. In this paper, we deal primarily with our data on pulmonary complications and hepatic dysfunction observed with mycoplasmal pneumonia.

MATERIALS AND METHODS

Pleural Effusion

The incidence of pleural effusion occurring in mycoplasmal pneumonia patients during the past 16 years was examined. A clinical comparison was made of the patients with pleural effusion and the patients with no complications.

Bacterial Superinfection

We carried out experimental and clinical studies with regard to bacterial superinfection. MAC strain cells of M. pneumoniae, which had been passed through hamsters, were shake-cultured in PPLO broth. Then the broth culture, containing...
10^3 to 10^4 CFU/ml of these cells, was used to infect hamsters by means of nasal spraying. After leaving these animals undisturbed for a fixed period of time (see below), a bacterial suspension containing 1.5 × 10^2 CFU/ml of a clinical isolate of *Staphylococcus aureus* (hereafter abbreviated as *S. aureus*), which had been passed through the peritoneal cavity of mice, was used to infect the hamsters intranasally. As a control, other hamsters were infected with the same amount of inoculum of *S. aureus* cells only. After a certain time, both groups of these animals were sacrificed and compared by means of bacteriological and pathological studies.

Following the infection with *M. pneumoniae*, the animals were infected with *S. aureus* after one, two, or three weeks. Differences in the cell counts as a function of the time of the superinfection were investigated.

The pathological findings, expressed as a score, were compared with the time interval. A score of 1.0 indicated a mild degree of bronchial pneumonia involving a small number of bronchi and alveoli. A score of 2.0 showed a moderate degree of bronchial pneumonia with a certain extent of spread. Finally, a score of 3.0 meant pulmonary findings that showed a severe degree of bronchial pneumonia with extensive involvement and also abscess formation in some parts.

Bacteriological studies were carried out on the sputum obtained from 137 human patients diagnosed as having mycoplasmal pneumonia. The patients were divided into three categories on the basis of their sputum isolates: normal flora, gram-positive cocci, or gram-negative rods; their clinical pictures were compared.

**Viral Superinfection**

In Nagasaki, 262 mycoplasmal pneumonia patients were tested for the presence of viral antibody titers.

In 1980, there had been an epidemic of mycoplasmal pneumonia in Fukue City on a small, distant island. At that time, an investigation was carried out on the patients' serum antibody titers for viruses, and the findings were summarized.

**Liver Function Disturbance**

After excluding patients with a past history of liver disease and with hepatitis-associated antigen, 213 patients diagnosed as having mycoplasmal pneumonia were investigated in terms of hepatic function. A comparison of each patient's clinical status with respect to the presence or absence of liver function abnormalities was made. The course taken by GOT and GPT values of the three patients from whom liver biopsies were taken was compared; also investigated were the histological changes in the biopsied liver tissues.

**RESULTS AND DISCUSSION**

**Pleural Effusion**

Our group found a transient, small amount of pleural effusion in 16 of 460 mycoplasmal pneumonia patients (approximately 4 percent). However, at Nagasaki in 1979, during a clinical study of an epidemic of mycoplasmal pneumonia, pleural effusion was observed as a complication in 13 of 113 patients, an incidence of 11.5 percent. Hers and Masurel [9] described small pleural effusions in 10 of 82 patients with *M. pneumoniae* pneumonia; Fine et al. [10] reported a figure of 21 percent and Stenstrom et al. [11] 11 percent. Isolation of *M. pneumoniae* from pleural fluid was reported in only one case by Nakao et al. [12].

Pain in the chest was noted in approximately half of the patients with pleural effusion, and the clinical course of the infection was also extended.
The length of time required for disappearance of the patients' pleural effusion was two weeks or more.

**Bacterial Superinfection**

**Experimental Studies**  The number of strains of *S. aureus* in the lungs was found to be highest in the case of the hamsters that had been infected with *S. aureus* one week after infection with *M. pneumoniae*, as compared with the other animal groups.

Figure 1 shows a comparison of the cell counts of *S. aureus* in the hamsters' lungs as a result of the following procedures: (1) The animals were first infected with *M. pneumoniae* by means of a nasal spray, and then, after a one-week period, they were infected with *S. aureus* via the nose, and (2) the animals were infected with *S. aureus* alone. In the animal group infected with *S. aureus* alone, the bacterial count was $3.2 \times 10^6$ on the second day after the nasal infection, and *S. aureus* had disappeared by the fifth day. Following the infection, it is evident the invading cells were cleared from the lungs. On the other hand, in the animal group that had first been infected with *M. pneumoniae*, the *S. aureus* cell count in the lungs on the second day was $1.9 \times 10^6$, and the cells of this bacterium could still be detected on the fifth and sixth days after infection.

In the group of animals that were first infected with *M. pneumoniae* and then infected with *S. aureus*, there was a tendency for the pathological findings to be more severe as compared with the findings in the group infected with *S. aureus* alone (Fig. 2).

Accordingly, as we have seen, in these animal experiments, hamsters infected with both *M. pneumoniae* and *S. aureus* suffered worse results as hosts in both
bacteriological and pathological terms. Moreover, Liu et al. [13] described an enhancement by *M. pneumoniae* of the development of type 1 pneumococcal septicemia in hamsters experimentally infected with both agents.

**Clinical Studies**

Gram-positive coci were isolated from 17, or 12.4 percent, of the human cases, with *S. aureus* the most common, since it was detected in the sputum from seven patients. Gram-negative rods were isolated from 21, or 15.3 percent, of the cases; these included six cases of *Hemophilus influenzae* and five cases of *Klebsiella pneumoniae*. A fever of 38°C or higher, acceleration of the blood sedimentation rate, leukocytosis, and so on were commonly seen in positive GPC or GNR groups, and these also showed a tendency for abnormal chest shadows to continue for a longer period of time.

**Viral Superinfection**

Thirty-seven percent of the cases of mycoplasmal pneumonia in Nagasaki showed significant sero-conversion for viruses. Elevated antibody titers against various viruses (such as RS virus) were detected in 11 of 28 of the patients, or 39.3 percent. At the same time, 49 patients diagnosed as having non-mycoplasmal pneumonia were also checked, and 35.4 percent of their sera contained similar elevated levels of antibodies to viruses. Accordingly, there appeared to be no special tendency for mycoplasma pneumonia to be accompanied by a higher frequency of superinfection with viruses. In addition, when the incidence of serologically verified multiple infections is discussed, the possibility of anamnestic serological responses being involved [7,8,14] must be considered.

**Liver Function Disturbance**

It was found that 77, or 36.2 percent, of these patients showed some kind of hepatic function abnormality during the course of the mycoplasmal pneumonia. An abnormality was detected at initial examination in 59 patients, while 14 first showed an abnormality at the end of one week, and four others had an abnormality at the end of the second week. During the course of therapy for the pneumonia, the highest values detected for liver function abnormalities were 182 for GOT, 242 for GPT, and 1.4 mg/dl for total bilirubin. The patients with hepatic function abnormalities showed a tendency to have a higher incidence of abnormalities of body temperature, leucocyte count, and CRP.

In Case 1, after the first week GOT values were elevated and parallel to GPT values. In the other two cases, however, GOT values gradually decreased and became normalized. GPT increased in Case 1 in the first week, and increased in Case 3 in the third week, but GPT values had returned to normal in all three patients by the fourth week. The pathological findings in the liver biopsies showed a certain degree of difference, but in all cases the diagnosis was non-specific reactive hepatitis. The structure of the lobules of the liver was seen to be normal, although there was a mild degree of lymphocyte infiltration in Glisson's capsule, and there was not much severe degeneration or necrosis of the hepatic cells. Nevertheless, scattered single-cell necrosis and focal necrosis could be seen, and these findings are indicative of so-called non-specific reactive hepatitis. Fraley et al. [2] also reported that the liver showed patchy cell necrosis and inflammatory cell infiltrates.
CONCLUSION

1. Data were presented on the pleural effusion, bacterial and viral superinfections, and hepatic dysfunction that have been found to accompany mycoplasmal infection.

2. The incidence of occurrence of the above-mentioned complications in the case of mycoplasmal pneumonia was as follows: pleural effusion, 4 percent; superinfections by bacteria, 28 percent; viral superinfections, 37 percent; and hepatic dysfunction, 36 percent.

3. In the patients who experienced these complications, there was a tendency for the clinical symptoms to be severe and for the course of recovery to be delayed.

4. Experiments were performed on mixed infections of *M. pneumoniae* and *S. aureus* in hamsters. When the animals were first infected with *M. pneumoniae* and then with *S. aureus*, both the bacteriological and pathological changes were more extensive than in the case of animals infected with *S. aureus* only.

5. Liver biopsies were performed on three human patients showing complications of hepatic dysfunction. Observations of the excised liver tissues resulted in a diagnosis of non-specific reactive hepatitis for each case.

REFERENCES

1. Cassel GH, et al: Mycoplasmas as agents of human disease. New Eng J Med 304:80–89, 1981
2. Fratley DS, Ruben FL, Donnelly EJ: Respiratory failure secondary to Mycoplasma pneumoniae infection. Southern Med J 72:437–440, 1979
3. Fischman RA, et al: Adult respiratory distress syndrome caused by Mycoplasma pneumoniae. Chest 74:471–473, 1978
4. Izumikawa K, Suzuyama Y, Hara K, et al: Lung function in adults with mycoplasmal pneumonia. Jap J Med 21:17–21, 1982
5. Clyde WA Jr: Neurological syndromes and mycoplasmal infections. Arch Neurol 37:65–66, 1980
6. Yamane Y, Kawai C: Myocarditis caused by Mycoplasma pneumoniae. Jap Circulation J 42:1279–1287, 1978
7. Sommergruber D: Incidence of Mycoplasma pneumoniae infections in the western districts of the country of Karl-Marx-Stadt in the period from 1974 to 1977. Z Gesamte Hyg 25:935–939, 1979
8. Ponka A: Occurrence of serologically verified Mycoplasma pneumoniae infections in Finland and in Scandinavia in 1970–1977. Scand J Infect Dis 12:27–31, 1980
9. Hers JFP, Masurel N: Infection with Mycoplasma pneumoniae in civilians in the Netherlands. Ann NY Acad Sci 143:447–460, 1967
10. Fine NL, Smith LR, Sheedy PR: Frequency of pleural effusion in mycoplasma and viral pneumonias. New Eng J Med 283:790–793, 1970
11. Stenstrom R, Jansson E, von Essen R: Mycoplasma pneumonia. Acta Radiologica 12:833–841, 1972
12. Nakao T, Orii T, Umetsu M: Mycoplasma pneumoniae pneumonia with pleural effusion, with special reference to isolation of Mycoplasma pneumoniae from pleural fluid. Tohoku J Exp Med 104:13–18, 1971
13. Liu C, Jayanetra P, Voth DW, et al: Potentiating effect of Mycoplasma pneumoniae infection on the development of pneumococcal septicemia in hamsters. J Infect Dis 125:603–612, 1972
14. Muller G, Schwochow D, Schwochow G, et al: Acute respiratory diseases in out-patients caused by mycoplasm and viruses. Z Gesamtte Hyg 24:759–762, 1978