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Factors Related to the Relapse of Bronchiolitis Obliterans Organizing Pneumonia*

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Study objective: **The purpose of this study is to determine factors, including laboratory data, related to the relapse of bronchiolitis obliterans organizing pneumonia (BOOP).**
Design: **Retrospective study.**
Setting and Patients: **The medical files of Fukuoka University Hospital and Nishi Fukuoka Hospital patients from 1984 to 1996 were reviewed, and 18 cases of BOOP that had been diagnosed using transbronchial or open lung biopsy were selected for evaluation.**
Measurements: **The 18 cases were put into two groups composed of 7 patients who relapsed and 11 who did not relapse. Their clinical symptoms and laboratory data at first admission, including hemograms, blood chemistry tests, and pulmonary function tests were compared. Patients with or without associated diseases, such as collagen vascular diseases, were compared using the same parameters in order to examine the relationship between the associated diseases and BOOP relapse.**
Results: **The serum levels of total protein and albumin in patients who relapsed were significantly lower than in patients who did not relapse, respectively: 5.8 (range, 4.4 to 6.2) vs 6.3 (range, 4.5 to 6.8) g/dL, $p < 0.05$; and 2.9 (range, 2.5 to 3.4) vs 3.7 (range, 2.8 to 4.3) g/dL, $p < 0.01$. Levels of serum albumin in BOOP patients with associated diseases, however, were significantly lower than in those without associated diseases, respectively: 2.95 (range, 2.5 to 3.9) vs 3.65 (range, 2.8 to 4.3) mg/dL, $p < 0.05$. The fall in serum albumin levels in patients who relapsed, therefore, was probably due to associated diseases. The fact that 5 of 8 patients with associated diseases relapsed but only 2 of 10 without associated diseases relapsed suggests that a relationship exists between associated diseases and the prognosis of BOOP, although this finding was not statistically significant because of the small number of cases and the heterogeneity of the associated diseases. The most striking observation was that Pao_2 levels in patients who relapsed were significantly lower than in those who did not, respectively: 55.4 (range, 39.9 to 73.2) vs 78.0 (range, 48.4 to 89.4) mm Hg, $p < 0.05$. However, Pao_2 levels were not statistically different between patients with and without associated diseases, respectively: 66.0 (range, 45.4 to 78.8) vs 71.4 (range, 39.9 to 89.4) mm Hg.**
Conclusions: **The severity of hypoxemia at first medical examination may be an important determinant for the subsequent BOOP relapse.** ***(CHEST 1998; 114:1599–1606)***

Key words: associated disease, steroid, relapse; bronchiolitis obliterans organizing pneumonia; cryptogenic organizing pneumonia

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia; COP = cryptogenic organizing pneumonitis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; RA = rheumatoid arthritis; TBLB = transbronchial lung biopsy; VC = vital capacity

Bronchiolitis obliterans organizing pneumonia (BOOP),[1] or cryptogenic organizing pneumonitis (COP),[2] is a pulmonary lesion characterized by subacute illness with preceding flu-like symptoms and distinctive pathologic findings. It has a wide spectrum of radiologic findings, ranging from multiple patchy, alveolar, or ground-glass infiltrates to diffuse reticulonodular opacities.

Histologic characteristics include buds of granulation tissue in alveoli and alveolar ducts, the infiltration of alveolar walls by mononuclear cells, alveolar space foam cells, and the absence of honeycombing or extensive interstitial fibrosis (preservation of alveolar structure).[1–3] In some instances, BOOP is associated with various systemic diseases[2] such as collagen-vascular diseases including rheumatoid arthritis (RA) and dermato-

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myositis. It is also associated with the inhalation of cocaine or therapeutic drugs such as cephalosporins,[4] and with hematologic disorders.[5]

With steroid therapy, BOOP has a good prognosis.[1–3] However, some cases progress rapidly and have a poor prognosis.[6] In addition, some patients relapse when the dose of prednisolone is reduced.[2] In this study, we presented 18 cases of BOOP, comparing those with and without relapse. Differences in clinical characteristics between these two groups were also evaluated.

Materials and Methods

We reviewed the medical files of patients admitted to the Second Department of Internal Medicine and the Second Department of Surgery at Fukuoka University Hospital from 1984 to 1996, and of those patients admitted to the Department of Internal Medicine at Nishi Fukuoka Hospital from 1992 to 1996. From these files we found 41 patients with conditions clinically diagnosed at discharge as "COP/BOOP" or "organizing pneumonia," who had undergone open lung biopsy, surgical resection, or transbronchial lung biopsy (TBLB) for histologic examination. We reviewed the histopathologic specimens and clinical information, and selected 18 cases that were pathologically confirmed as COP/BOOP. Their specimen findings were consistent with COP/BOOP: intraluminal organized polyps in peripheral airways without necrosis, granuloma, or aggregates of neutrophils. These 18 patients became the subjects in the present study. Patients with conditions diagnosed as "suspected" BOOP at discharge that did not undergo open lung biopsy, surgical resection, or TBLB were excluded, as were many with necrosis or aggregates of neutrophils in their specimens suggesting the healing stage of bacterial pneumonia or abscess (Table 1).

The selected patients were assigned case numbers. Patients who had relapsed were put into one group, and patients who had not relapsed were put into another group. Clinical symptoms and signs, and laboratory data of both groups at the time of hospitalization were compared in order to find any underlying etiology for relapse. These parameters were also compared in patients with or without associated diseases in order to find any relationship between associated diseases and relapse (Table 2). Other criteria examined were the periods between the onset of symptoms and admission, the follow-up periods after admission, and the steroid regimen, if administered. Of those seven patients who relapsed (cases 12 to 18), additional information was recorded: for cases 12 to 17, the length of time between the start of steroid therapy and relapse; and for case 18, the length of time from first admission to relapse.

The diagnosis of BOOP was made using the following determinants: abnormal chest radiograph findings ranging from multiple acinar/nodular shadows to solitary pneumonia-like or nodular shadows; histopathologically, the presence of intraluminal fibrotic buds within the alveoli and alveolar ducts with or without bronchiolar involvement, and infiltration of chronic inflammatory cells in the alveolar septa with preservation of the alveolar structure.[1–3] A poor response to antibiotics and a good response to steroids supported the diagnosis. Relapse was defined as the reappearance of abnormal shadows or the appearance of newly formed abnormal shadows on chest radiograph that are characteristic of BOOP. All patients who relapsed had increased serum C-reactive protein (CRP) levels and increased erythrocyte sedimentation rate (ESR) at the time of relapse. Of the seven patients who relapsed, relapse was confirmed by TBLB in cases 13 and 18; steroids were effective in cases 12, 15, 16, and 17; and case 14 had a deteriorated course despite the aggressive therapy of steroids and antibiotics.

Statistical Analysis

Laboratory and pulmonary function data are expressed as medians and ranges. Data comparisons were made using the Mann-Whitney U test. Clinical symptoms and signs, such as cough and sputum, were evaluated using the Fisher exact test. Linear regression analysis was performed to examine the relationship between serum levels of cholesterol and Pao_2. A value of $p < 0.05$ was considered to be statistically significant.

Table 1—*Selection Criteria of Patients

1. Patients who were admitted in
   Second Department of Internal Medicine, Fukuoka University Hospital from 1984 to 1996
   Second Department of Surgery, Fukuoka University Hospital from 1984 to 1996
   Department of Internal Medicine, Nishi Fukuoka Hospital from 1992 to 1996
2. Patients who have a clinical diagnosis at discharge of COP/BOOP or "organizing pneumonia" using open lung biopsy, surgical resection, or TBLB pathologic analysis
3. Cases histologically confirmed as COP/BOOP using open lung biopsy, surgical resection, or TBLB with the help of clinical informations
4. Exclude cases who have histologic findings inconsistent with those in COP/BOOP, such as destruction of alveolar structures, necrosis, granuloma, or aggregates of neutrophils

*Patients who meet criteria 1, 2, and 3 are the subjects in the present study.

Results

Patient Profile

Gender, age, associated disease, and the period from the onset of illness to admission were among factors studied in the two groups (Table 2). Seven patients relapsed (cases 12 to 18) and 11 did not relapse (cases 1 to 11). Of the patients who relapsed, two died: one from the progression of BOOP (case 14), and one from a cerebral hemorrhage (case 15) during the tapering period of prednisolone. Five patients improved at the time of relapse when their steroid therapy was increased or restarted (Table 2).

Actual follow-up periods were not significantly different for patients who did or did not relapse, respectively: 1.92 (range, 1.00 to 6.17) vs 2.67 (range, 0.08 to 11.42) years. There were no significant differences in age between patients who did or did not relapse, respectively: 66 (range, 61 to 79) vs 68 (range, 50 to 80) years old. Nor were there significant differences in the period from onset of symptoms to first admission between patients who did or did not relapse, respectively: 30 (range, 5 to 120) vs

Table 2—*BOOP Patients With and Without Relapse

Case No.	Gender/Age at Entry, yr	Associated Diseases of Entry	Period From Onset of Symptom to Admission, d	Follow-up Period From First Admission/Start of Steroid Therapy to Relapse†	Total Dose of Prednisolone For the First Month, mg‡
1	M/57§		14	7 yr	NA§
2	M/68		70	2 yr, 8 mo	2,570
3	M/74	Multiple myeloma past history of operated thyroid cancer	10	1 yr	NA
4	M/80		60	1 mo	NA
5	F/50	Rheumatoid arthritis	7	3 yr	1,600
6	F/52		100	11 yr, 5 mo	NA
7	F/56	Hepatitis C	50	6 yr, 2 mo	4,490
8	F/66		52	4 yr, 9 mo	845
9	F/69		40	35 d	NA
10	F/76		13	1 mo	NA
11	F/77			2 yr	NA
12	M/61		8	6 yr, 2 mo/36 d	375
13	M/62	Dilated cardiomyopathy	30	4 yr, 1 mo/2 yr	650
14	M/66	NIDDM Hepatitis C	30	1 yr/7 mo‖	3,480
15	M/70	Myeloproliferative disorder	5	1 yr, 6 mo/88 d‖	6,585
16	F/62		120	5 yr, 11 mo/3 yr	3,645
17	F/66	Chronic glomerulonephritis	50	1 yr, 9 mo/34 d	773
18	F/79	Rheumatoid arthritis Hypothyroidism	7	1 yr, 11 mo/3 mo¶	NA

*Cases 1 to 11 are those without relapse, and cases 12 to 18 are those with relapse.
†Cases 12 to 17.
‡Steroids other than prednisolone were converted to the dose of prednisolone (5 mg prednisolone = 4 mg methylprednisolone = 20 mg hydrocortisone).
§F = female; M = male; NA = not administered; NIDDM = non-insulin-dependent diabetes mellitus.
‖Died during the tapering period of the steroid.
¶Period from admission to relapse.

45 (range, 7 to 100) days (Mann-Whitney U test). Eight of our 18 patients had associated diseases such as RA, thyroid disease, multiple myeloma, or myeloproliferative disorder; and 10 had no associated diseases. Five of the 8 patients with associated diseases and 2 of the 10 without associated diseases relapsed, and 5 of the 7 patients who relapsed had associated diseases.

The total dose of prednisolone or its equivalent was compared, and during the first month of steroid therapy no significant differences were found between patients who did or did not relapse, respectively: 773 (range, 0 to 6,585) vs 0 (range, 0 to 4,490) mg. Six of the 7 patients who did relapse received steroid therapy, and 4 of the 11 who did not relapse received steroid therapy (Table 2). Eight of the 18

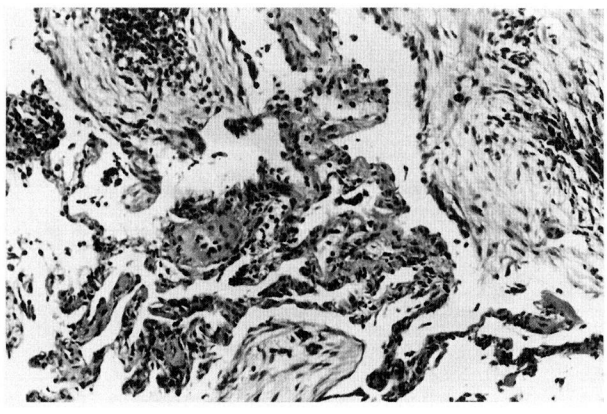

FIGURE 1. TBLB specimen from case 13. Polypoid fibrous tissue plugs were found in distal airspaces. Many mononuclear cells were infiltrated in the center of the plugs (hematoxylin-eosin, original magnification ×99).

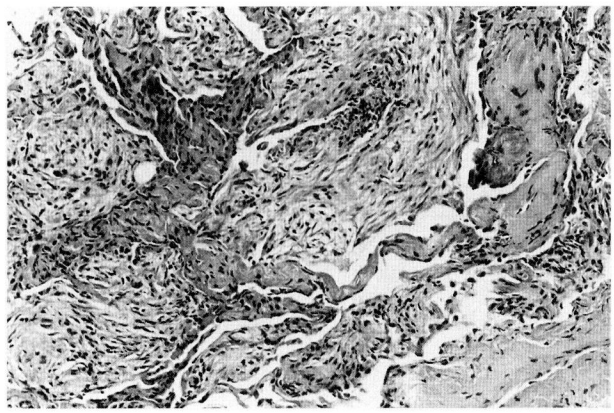

FIGURE 2. TBLB specimen from case 14. Distal airspaces were filled with loose connective tissue (hematoxylin-eosin, original magnification ×99).

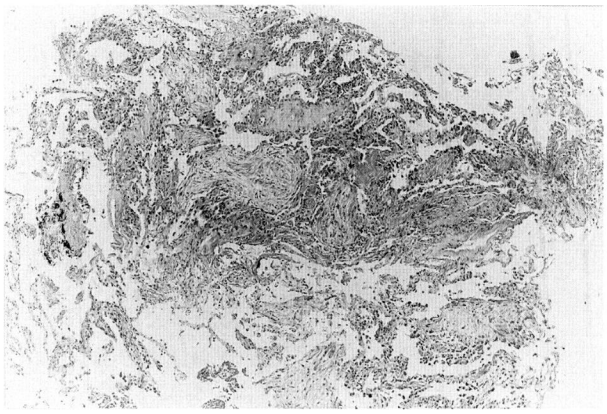

FIGURE 3. TBLB specimen from case 16. Distal airspaces were filled with loose connective tissue. Alveolar septa were mildly thickened with mononuclear cell infiltration (hematoxylin-eosin, original magnification ×40).

total patients were not given steroid therapy, and its use was decided by each physician in charge. In these eight patients, BOOP was considered to be relatively less severe.

Pathologic Analysis

Pathologic diagnosis was based on open lung biopsy in 4 patients, surgical resection in 1, and TBLB in 13, according to the criteria described above. TBLB specimens in three patients who relapsed (cases 13,14, and 16) showed intraluminal polyps of loose connective tissues in peripheral airspaces with mildly thickened alveolar septa with mononuclear cell infiltration (Figs 1–3). The specimen from case 13 was obtained at the time of relapse, and the specimens from cases 14 and 16 were taken at first hospitalizations.

Clinical and Laboratory Data

Clinical findings including height, weight, symptoms, and crackles of the patients who had relapsed were compared with data from the patients who had not relapsed; and the clinical findings of the patients with associated diseases were compared with data from the patients without associated diseases (Table 3). All of the patients had respiratory symptoms such as cough or dyspnea. All of the patients but one, (case 1) who had a solitary nodular shadow, had multiple acinar or nodular shadows on chest radiograph. Fever was more frequent in 6 of the 7 patients who relapsed than in 2 of the 11 who did not relapse ($p < 0.05$, the Fisher exact test). Although sputum and dyspnea were found more frequently in patients who relapsed than in those who did not, no statistical significance was noted.

Laboratory data including hemogram, blood chemistry, spirogram, and arterial blood gas analysis at the time of initial presentation are shown in Tables 4–7. The serum levels of total protein and albumin, and the albumin-globulin ratio in patients who relapsed were significantly lower than in patients who did not relapse, respectively: 5.8 (range, 4.4 to 6.2) vs 6.3 (range, 4.5 to 6.8) g/dL, $p < 0.05$; 2.9 (range, 2.5 to 3.4) vs 3.7 (range, 2.8 to 4.3) g/dL, $p < 0.01$; and 1.1(range, 0.70 to 1.75) vs 1.63 (range, 1.03 to 1.95), $p < 0.05$. However, serum levels of albumin and albumin-globulin ratio in patients with associated diseases were significantly lower than in patients without associated diseases, respectively: 2.95 (range, 2.5 to 3.9) vs 3.65 (range, 2.8 to 4.3) mg/dL, $p < 0.05$; and 1.15 (range, 0.70 to 1.65) vs 1.515 (range, 1.07 to 1.95) mg/dL, $p < 0.05$ (Table 5). Therefore, the fall in serum albumin level in patients who relapsed seems to be largely due to associated diseases. Five of the 7 patients who relapsed had associated diseases such as thyroid disease, myeloproliferative disorder, or RA; however, only 3 of the 11 patients who did not relapse had associated diseases. Associated diseases, therefore, appear to

Table 3—*Symptoms and Signs of Patients With BOOP*

	Height/Range, cm*	Weight/Range, kg	BMI/Range†	Cough‡	Sputum	Fever	Dyspnea	Crackles
Patients without relapse (n = 11)	157/143–165	52/41–71	22/18–33	10	4	2	5	5
Patients with relapse (n = 7)	157/147–165	48/42–62	19/17–24	7	5	6	5	6
p Value§	NS	NS	NS	NS	NS	< 0.05	NS	NS
Patients without associated diseases (n = 10)	158.5/143–165	52/41–64	20.5/17–27	9	4	3	4	6
Patients with associated diseases (n = 8)	156.5/146–165	51.5/47–71	21.5/19–33	7	5	4	6	7
p Value	NS	NS	NS	NS	NS	NS	NS	NS

*Height, Weight, and BMI are expressed as medians and ranges.
†BMI = body mass index; NS = not significant.
‡Values for Cough, Sputum, Fever, Dyspnea, and Crackles show number of patients with these symptoms and signs; analyzed by Fisher exact test.
§Analyzed by Mann-Whitney *U* test.

Table 4—*Laboratory Data of Patients With BOOP*

	Hb/Range, g/dL* (13.4–17.6)†	WBC/Range, mm^3 (3,900–9,300)	Eosinophils/Range, % WBC (2.0–4.0)	ESR/Range, mm/h	CRP/Range, mg/dL (> 0.2)	LDH/Range, IU/L (260–485)
Patients without relapse (n = 11)	11.6/9.9–13.9‡	5,300/3,500–8,100	4.0/1.0–10.5	30/10–101	0.2/0.0–8.4	339/300–771
Number of patients studied	11	11	11	11	9	11
Patients with relapse (n = 7)	10.0 /6.8–13.1	5,400 /4,300–22,500	4.0 /0.0–12.0	77 /14–115	3.9 /0.0–25.5	544 /288–760
Number of patients studied	7	7	7	6	7	7
p Value§	NS	NS	NS	NS	NS	NS
Patients without associated diseases (n = 10)	12.5 /9.9–13.9	4,950 /3,500–13,800	4.5 /0.0–12.0	39 /10–115	0.25 /0.0–25.5	317 /300–634
Number of patients studied	10	10	10	10	8	10
Patients with associated diseases (n = 8)	11.0 /6.8–11.8	6,200 /4,100–22,500	3.95 /1.0–7.7	63 /14–108	2.9 /0.0–21.0	585 /288–771
Number of patients studied	8	8	8	7	8	8
p Value	NS	NS	NS	NS	NS	< 0.05

*Hb = hemoglobin; NS = not significant.
†Values in parentheses indicate normal range.
‡All data expressed as medians and ranges.
§Analyzed by Mann-Whitney *U* test.

be related to the prognosis of BOOP; but the Fisher exact test did not show statistical significance.

PaO_2 levels in patients who relapsed were significantly lower than in patients who did not relapse, respectively: 55.4 (range, 39.9 to 73.2) vs 78.0 (range, 48.4 to 89.4) mm Hg, $p < 0.05$). However, PaO_2 levels in patients with associated diseases were not significantly different from levels in patients without

Table 5—*Laboratory Data of Patients With BOOP*

	Total Protein/Range, g/dL (6.7–8.3)†	Albumin/Range, g/dL (4.0–5.0)	Albumin-Globulin/ Range (1.3–2.1)	GOT*/Range, IU/L (33 >)	GPT/Range, IU/L (35 >)	Alkaline Phosphatase/Range, IU/L (115–360)
Patients without relapse (n = 11)	6.3/4.5–6.8‡	3.7/2.8–4.3	1.63/1.03–1.95	15/12–119	12/7–132	191.5/127–1,335
Number of patients studied	11	11	11	11	11	11
Patients with relapse (n = 7)	5.8/4.4–6.2	2.9/2.5–3.4	1.1/0.70–1.75	21/12–72	9/6–46	144/92–556
Number of patients studied	7	7	7	7	7	7
p Value§	< 0.05	< 0.01	< 0.05	NS	NS	NS
Patients without associated diseases (n = 10)	6.15/4.4–6.8	3.65/2.8–4.3	1.515/1.07–1.95	15/12–119	8/7–132	191.5/136–1,335
Number of patients studied	10	10	10	10	10	10
Patients with associated diseases (n = 8)	5.9/4.5–6.5	2.95/2.5–3.9	1.15/0.70–1.65	21/12–72	16.5/6–46	141/92–556
Number of patients studied	8	8	8	8	8	8
p Value	NS	< 0.05	< 0.05	NS	NS	NS

*GOT = glutamic oxalacetic transaminase; GPT = glutamic pyruvic transaminase; NS = not significant.
†Values in parentheses indicate normal range.
‡All data expressed as medians and ranges.
§Analyzed by Mann-Whitney *U* test.

Table 6—*Laboratory Data of Patients With BOOP*

	BUN/Range, mg/dL (8–22)*	Creatinine/Range, mg/dL (0.6–1.1)	Na/Range, mEq/L (138–146)	K/Range, mEq/L (3.6–4.9)	Cholesterol/Range, mg/dL (130–220)	Uric Acid/Range, mg/dL (3.6–7.0)	Glucose/Range, mg/dL (70–105)
Patients without relapse (n = 11)	15/9–27†	0.70/0.3–2.8	143/141–146	4.1/3.4–4.5	186/156–229	5.1/2.6–7.8	88/73–96
Number of patients studied	11	11	11	11	11	11	11
Patients with relapse (n = 7)	19/11–101	0.8/0.5–11.0	140/133–147	4.1/4.0–5.5	114/97–184	5.1/2.4–8.6	121/75–146
Number of patients studied	7	7	7	7	7	7	7
p Value‡	NS§	NS	< 0.05	NS	< 0.01	NS	NS
Patients without associated diseases (n = 10)	14.5/9–21	0.7/0.3–1.0	143/140–146	4.1/3.8–4.5	172.5/97–218	4.65/2.4–7.8	85/73–144
Number of patients studied	10	10	10	10	10	10	10
Patients with associated diseases (n = 8)	22.5/10–101	0.85/0.4–11.0	141/133–147	4.15/3.4–5.5	161/103–229	6.3/3.4–8.6	95/82–146
Number of patients studied	8	8	8	8	8	8	8
p Value	< 0.05	NS	NS	NS	NS	NS	NS

*Values in parentheses indicate normal range.
†All data expressed as medians and ranges.
‡Analyzed by Mann-Whitney *U* test.
§NS = not significant.

associated diseases, respectively: 66.0 (range, 45.4 to 78.8) vs 71.4 (range, 39.9 to 89.4) mm Hg (Table 7). A positive correlation was shown to exist between serum levels of cholesterol and Pa_{O_2} in all patients ($r = 0.616$, $p < 0.01$; Fig 4). The serum levels of cholesterol in patients who relapsed were significantly lower than in patients who did not relapse, respectively: 114 (range, 97 to 184) vs 186 (range, 156 to 229) mg/dL, $p < 0.01$. There were no significant differences in serum cholesterol levels between patients with or without associated diseases (Table 6).

Lactate dehydrogenase (LDH) and BUN levels (Tables 4, 6) in patients with associated diseases

Table 7—*Spirogram and Arterial Blood Gas Analysis of Patients With BOOP*

	VC,* mL	%VC	FEV_1, mL	FEV_1, %	Pa_{O_2}, mm Hg	Pa_{CO_2}, mm Hg
Patients without relapse (n = 11)	2,220/1,590–3,440†	92/71–112	1,590/1,130–2,690	75/65–92	78.0/48.4–89.4	39.4/34.0–48.4
Number of patients studied	9	9	9	9	10	10
Patients with relapse (n = 7)	2,370/1,940–2,750	95/82–102	1,850/1,530–1,860	74.5/71–78	55.4/39.9–73.2	35.8/32.2–41.4
Number of patients studied	3	3	3	3	7	7
p Value‡	NS	NS	NS	NS	< 0.05	NS
Patients without associated diseases (n = 10)	2,295/1,590–3,440	98/71–112	1,725/1,130–2,690	75.5/65–92	71.4/39.9–89.4	38.3/33.6–48.4
Number of patients studied	8	8	8	8	9	9
Patients with associated diseases (n = 8)	2,255/1,940–2,750	90.5/82–95	1,635/1,530–1,850	74.0/71–75	66.0/45.4–78.8	38.4/32.2–41.4
Number of patients studied	4	4	4	4	8	8
p Value	NS	NS	NS	NS	NS	NS

*VC = vital capacity.
†All data expressed as medians and ranges.
‡Analyzed by Mann-Whitney *U* test.

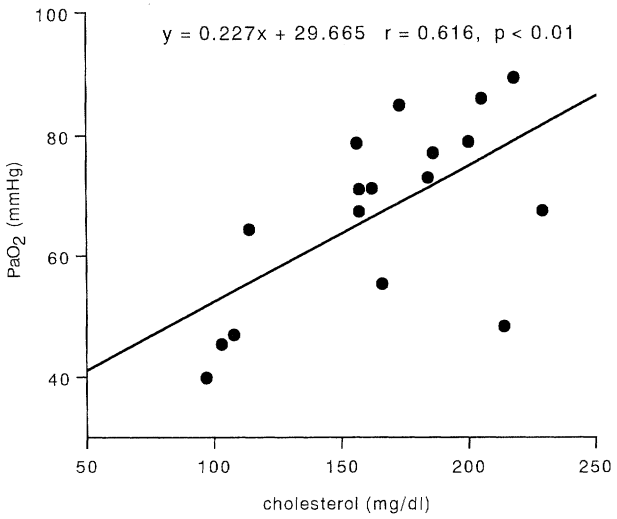

FIGURE 4. Correlation between PaO_2 and serum levels of cholesterol. PaO_2 was correlated with serum levels of cholesterol and could be expressed as $y = 0.227x + 29.665$ ($r = 0.616$, $p < 0.01$).

were significantly higher than in patients without associated diseases, respectively: 585 (range, 288 to 771) vs 317 (range, 300 to 634) IU/l, $p < 0.05$; 22.5 (range, 10 to 101) vs 14.5 (range, 9 to 21) mg/dL, $p < 0.05$. There were no significant differences in the vital capacity (VC) or FEV_1 between the groups (Table 7). However, only three patients underwent spirographic analysis and relapsed, and this may not be enough to show significance.

DISCUSSION

Since Epler et al[1] proposed BOOP as a clinicopathologic entity, a number of reports about BOOP have been published. Two years prior to Epler's report, Davison et al[2] presented eight patients with histologic intra-alveolar organization (organizing pneumonia) without evidence of an infective or other etiological agent, and they named the disorder cryptogenic organizing pneumonitis (COP). Today it is widely believed that BOOP, as defined by Epler et al,[1] is essentially the same disease as COP, as defined by Davison et al,[2] and bronchiolitis interstitial pneumonia, as defined by Libel and Carrington.[7]

In our study, the pathologic diagnosis of BOOP was made using TBLB in 13 cases, and by open lung biopsy or surgical resection in 5 others. Although an open lung biopsy is considered to be the best way to obtain a representative lung specimen,[8] TBLB has been reported to be sufficient unless the clinical features, including the chest radiographic findings and the response to antibiotics or steroids, are not consistent with COP.[5, 9–11] Prior to treatment with steroids, cases 2, 5, 12, 13, 14, 15, and 17 were treated with antibiotics without effect. Antibiotics were also ineffective in cases 10 and 18.

Steroid therapy yields an excellent response in most BOOP patients, but some conditions are refractory or worsen after a transient positive response.[2, 8, and 12] Moreover, some patients with BOOP have associated diseases such as collagen vascular diseases, making careful treatment and follow-up necessary, especially when BOOP is associated with systemic diseases such as lymphoproliferative or connective tissue diseases.[13]

The rate of BOOP relapse in our study seems high, compared to studies by other investigators.[14] Perhaps this is because all of our subjects were observed and treated as inpatients. It is noteworthy, however, that five of the seven patients in our study who relapsed had associated diseases such as thyroid disease, RA, or myeloproliferative disorder. One patient (case 14), who died of progressive BOOP, had diabetes mellitus and hepatitis C. Cohen et al[6] have demonstrated that the prognosis is poor when BOOP is associated with a chronic disease, especially a connective tissue or autoimmune disease, or with exposure to drugs.[14] However, we could not demonstrate a significant relationship between associated diseases and relapse of BOOP, probably because of the small sample size and the heterogeneity of associated diseases.

It is difficult to conclude from the present study that hypoalbuminemia is a prognostic factor for BOOP, because the fall in this parameter is also demonstrated in patients with associated diseases. There were relatively higher levels of serum CRP and LDH, and increased ESR in patients who relapsed, compared with patients who did not relapse; but similar tendencies were observed between patients with and without associated diseases. Therefore, these abnormal findings may also be related to the associated diseases.

The most striking finding in the present study is that BOOP patients who relapsed had more severe hypoxemia than patients who did not relapse. Because there were no significant differences in PaO_2 levels between patients with or without associated diseases, hypoxemia, which may reflect the severity of the pulmonary disease at initial presentation, seems to be an important factor in the prognosis of BOOP.

Significantly lower levels of serum cholesterol were noted in patients who relapsed, and there were no significant differences in cholesterol levels between patients with or without associated diseases. Although it is difficult to clarify the significance of lower levels of cholesterol in patients who relapsed, cholesterol could be another important factor in

predicting the relapse of BOOP because serum cholesterol levels were positively correlated with PaO_2.

Relapse occurs frequently when the dose of prednisolone is reduced,[2,8,13] as seen in cases 12, 14, 15, and 17. There were no significant differences in the doses of prednisolone given during the first month of therapy to patients who did or did not relapse. However, 6 of the 7 patients who relapsed and 4 of the 11 patients who did not relapse required steroid therapy. An initial decision made by a clinician to administer, presumably based on disease severity, may be predictive of the subsequent course of the disease.

In conclusion, the severity of hypoxemia, which reflects the severity of BOOP, may be an important determinant for the subsequent relapse of the disease. Further investigation is needed to elucidate the relationship between associated diseases and BOOP relapse.

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