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Table 1. Summery Demographic and Clinical Characteristics of Subjects

Category	Subcategory	n/N(%) or median(IQR)
Male sex		156/215(73)
Age		67(50,79)
Nationality	Japanese	213(99)
Smear status	Positive	182(84)
Photographic findings	Cavitation	105(49)
Immunosuppressive therapy		18/215(12)
Bedridden		38/215(18)*
Malignancies		10/215(4.7)
Laboratory findings	WBC count cells/μL	6400(5000,8125)
	Lymphocyte count cells/μL	1132(635,1556)
	Serum albumin g/dL	3.3(2.5,3.9)
	CRP mg/dL	4.27(0.99,8.81)
	HbA1c %	5.9(5.4,6.3)

IQR:Inter-quartile range
* Among bedridden group, two people overlapped with malignancies group, and other two people overlapped with immunosuppressive therapy group.

Table 2. QFT-G and ELISPOT Results for All Study Participants

	QFT-G	ELISPOT	p-value*
Positive, n(%)	160(74)	199(93)	p<0.0001
Negative, n(%)	49(23)	16(7.4)	p<0.0001
Indeterminate, n(%)	6(2.8)	0(0)	ND

*p-value for differentce between QFT-G and ELISPOT analysis.

subgroups of 199 (93%) positive and 16 (7%) negative ELISPOT result patients, the median peripheral lymphocyte count was higher in the positive group (median: 1,172; IQR: 704, 1,587) than in the negative group (median: 616; IQR, 387, 1,178) (p=0.012).

Patient characteristics in various subgroups were as follows. Of 6 patients with indeterminate QFT-G results, 2 had malignancies, 1 of which was a terminal status of gastric cancer. Among the 16 with negative results for both QFT-G and ELISPOT, 5 (31%) were receiving immunosuppressive therapy, 6 (38%) were bedridden (1 of whom was also receiving immunosuppressive therapy), and 1 had a malignancy. Among the 33 patients with negative results for QFT-G and positive results for ELISPOT, 2 (6%) were receiving immunosuppressive therapy, 9 (27%) were bedridden, and 2 (6%) had malignancies. All patients with positive QFT-G results were also ELISPOT-positive. Of the 160 patients with positive results on both assays, 11 (7%) were receiving immunosuppressive therapy, 22 (14%) were bedridden (1 of whom was also receiving immunosuppressive therapy), and 1 had a malignancy (and was also bedridden).

Influence of lymphocyte count on performance of QFT-G and ELISPOT analyses

When the peripheral lymphocyte count was ≥1,000/μL, the sensitivity of both tests was high: QFT-G (88%, 114/129; 95% CI, 82-94%) and ELISPOT (97%, 125/129; 95% CI, 94-100%). However, a clear trend of decreasing sensitivity with decreasing peripheral lymphocyte count was evident for both QFT-G (test for trend p<0.0001) and ELISPOT (test for trend p=0.007). This decline was more notable for QFT-G than for ELISPOT. ELISPOT was 81% (25/31; 95% CI, 66-96%) sensitive even when the lymphocyte count was less than 500/μL, whereas QFT-G was less than 70% sensitive when the lymphocyte count was <1,000/μL and less than 39% (12/31; 95% CI, 21-57%) when the lymphocyte count was <500/μL (Fig. 3).

For further analysis of factors affecting sensitivity, QFT-G and ELISPOT results were transformed to binary variables by combining negative and indeterminate results after logistic regression analysis. In order to increase statistical power, continuous variables were redefined as dichotomous variables using the following cut-off values: age 67 years (arbitrary), serum Alb 3.3 g/dL and CRP 4.72 mg/dL (median of study population), lymphocyte count 1,000 cells/μL (definition of lymphocytopenia), and HbA1c 6.5% (recommended by the American Diabetes Association). Odds ratios for factors affecting positive QFT-G results are listed in Table 3. The following factors were associated with a positive QFT-G result: lymphocyte count greater than 1,000 cells/μL (by both univariate and multivariate analyses), serum Alb greater than 3.3 g/dL (by both univariate and multivariate analyses), CRP greater than 4.72 mg/dL (by univariate analysis only), and bedridden status (by univariate analysis only). On the other hand, odds ratios for factors affecting positive ELISPOT results are listed in Table 4. Factors associated with a positive ELISPOT result were a lymphocyte count of greater than 1,000 cells/μL (by both univariate and multivariate analyses), immunosuppressive therapy (by both univariate and multivariate analyses), and serum Alb of greater than 3.3 g/dL (by univariate analysis only).

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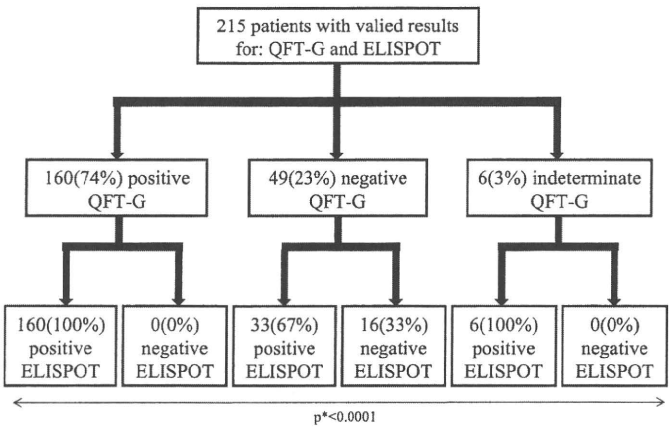

Figure 1. Distribution of ELISPOT results, according to results obtained with QFT-G. *P-values indicate the difference between positive, negative and indeterminate results for QFT-G, for Kruskal-Wallis exact test.

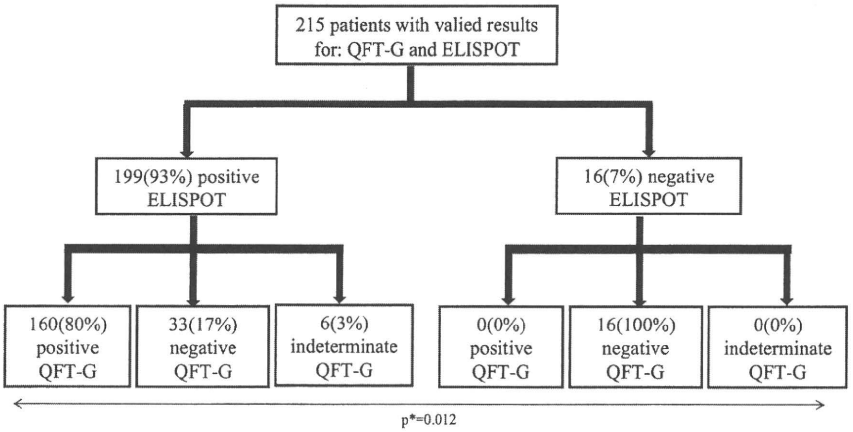

Figure 2. Distribution of QFT-G results, according to results obtained with ELISPOT. *P-values indicate the difference between positive and negative results for ELISPOT, for Mann-Whitney exact test.

Discussion

This is the first study that directs comparison of the sensitivity of 2 IGRA tests, QFT-G and ELISPOT, for detecting microbiologically determined pulmonary tuberculosis in patients, including HIV-negative immunocompromised hosts. We found that the sensitivity for the diagnosis of pulmonary tuberculosis is very high in both tests, and the sensitivity was not significantly confounded by age and gender. ELISPOT sensitivity, but not QFT-G sensitivity, was unaffected by nutritional state as indicated by the serum Alb levels.

This study evaluated the effect of peripheral blood lymphocyte count on QFT-G and ELISPOT and their sensitivity in patients with pulmonary tuberculosis, including immunocompromised hosts. The sensitivity of both tests was affected by lymphocyte counts, with a clear trend of a decrease in sensitivity with decreasing lymphocyte count. This was particularly marked in the case of QFT-G.

Overall sensitivity determined by this study was nearly identical to the results of the meta-analysis by Pai et al (5), which reported sensitivities of 78% for QFT-G and 90% for ELISPOT but appeared inconsistent with other reports (2, 5, 17, 18, 22, 23) in suggesting that ELISPOT is significantly more sensitive than QFT-G.

The correlation between peripheral lymphocyte count and the sensitivity of IGRAs has been reported previously in HIV-positive patients. In some earlier reports, QFT-G sensitivity correlated with CD 4 lymphocyte counts (8, 10, 11, 15, 24) but ELISPOT sensitivity was independent of it (19, 20, 25, 26). In this study, ELISPOT was more than 80% sensitive even when the lymphocyte count was less than 500/μL, whereas QFT-G was less than 70% sensitive when the lymphocyte count was <1,000/μL and less than 39% when the lymphocyte count was <500/μL. In addition, nearly identical tendencies were found in a population of HIV-negative immunocompromised patients.

The present study also indicated that the group of patients with negative and indeterminate results with QFT-G had a lower mean peripheral lymphocyte count, lower than the

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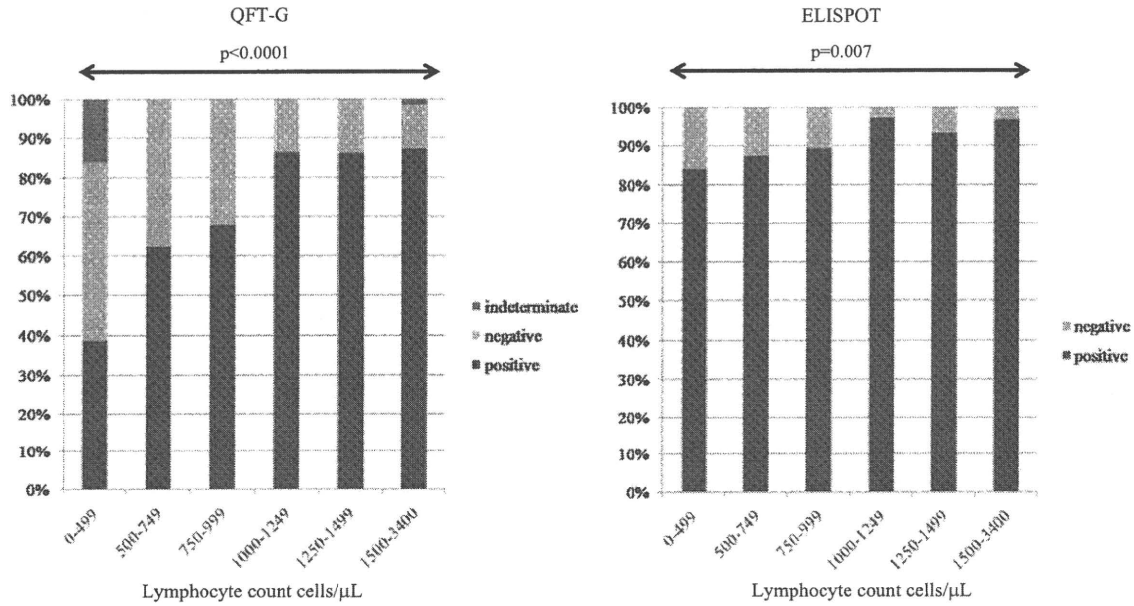

Figure 3. Influence of lymphocyte count on performance of the QFT-G and ELISPOT analysis in pulmonary tubercurosis patients. For all patients the % of positive, negative and indeterminate was grouped by the individual number of lymphocyte count cells/μL. p-values are for chi-square exact for linear trend. The number of patients in each lymphocyte count group was: 0-499:31, 500-749:30, 750-999:28, 1000-1249:37, 1250-1499:29, 1500-3400:60.

Table 3. Association of Risk Factors with a Positive QFT-G Results

Parameter	n	Univariate analysis		Multivariate analysis	
		OR(95% CI)	p	OR(95% CI)	p
lymphocyte count >1000 cells/μL	126	5.167(2.679-9.967)	<0.0001	3.788(1.861-7.708)	<0.0001
Male sex	156	0.751(0.371-1.523)	0.428	0.562(0.234-1.351)	0.198
Age >67 years	107	0.591(0.320-1.090)	0.092	1.180(0.511-2.721)	0.699
Alb >3.3 g/dL	98	3.908(1.971-7.746)	<0.0001	2.507(1.200-5.234)	0.013
CRP >4.72 mg/dL	100	0.395(0.208-0.750)	0.005	0.714(0.284-1.794)	0.714
HbA1c >6.5 %	39	1.555(0.672-3.599)	0.303	2.223(0.793-6.231)	0.129
Immunosuppressive therapy	18	0.517(0.190-1.405)	0.196	0.558(0.176-1.770)	0.322
Bedridden	38	0.400(0.192-0.831)	0.014	0.718(0.273-1.888)	0.502
Malignancies	10	0.329(0.092-1.182)	0.088	0.365(0.086-1.553)	0.173
Cavitation	105	1.572(0.852-2.898)	0.147	1.951(0.918-4.144)	0.082

OR:Odds Ratio. CI:Confidence interval.

Table 4. Association of Risk Factors with a Positive ELISPOT Results

Parameter	n	Univariate analysis		Multivariate analysis	
		OR(95% CI)	p	OR(95% CI)	p
lymphocyte count >1000 cells/μL	126	4.133(1.418-12.045)	0.009	3.314(1.100-9.990)	0.033
Male sex	156	1.054(0.359-3.096)	0.924	0.782(0.215-2.848)	0.709
Age >67 years	107	0.612(0.228-1.641)	0.329	1.760(0.447-6.934)	0.478
Alb >3.3 g/dL	98	3.524(1.110-11.182)	0.033	1.778(0.363-8.702)	0.478
CRP >4.72 mg/dL	100	0.396(0.135-1.167)	0.093	0.619(0.152-2.528)	0.504
HbA1c >6.5 %	39	1.159(0.319-4.204)	0.823	2.626(0.483-14.284)	0.268
Immunosuppressive therapy	18	0.179(0.055-0.579)	0.004	0.202(0.060-0.684)	0.01
Bedridden	38	0.376(0.132-1.076)	0.068	0.465(0.112-1.929)	0.292
Malignancies	10	0.793(0.095-6.635)	0.83	0.645(0.066-6.295)	0.706
Cavitation	105	2.000(0.723-5.536)	0.182	2.174(0.658-7.185)	0.203

OR: Odds Ratio. CI: Confidence interval

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group with positive results. Previously, HIV-positive patients with a positive QFT-G result were shown to have a significantly higher median CD4 lymphocyte count than those with a negative QFT-G (8, 11). Moreover, as the CD4 lymphocyte counts decreased, the number of indeterminate results increased (8, 10, 11). Our study also showed that patients with indeterminate QFT-G results had a significantly lower median peripheral lymphocyte count than those with determinate QFT-G results, and patients with negative results had a lower median peripheral lymphocyte count than patients with positive results with both QFT-G and ELISPOT.

Considering patient characteristics, 5 of 6 patients with indeterminate QFT-G results had lymphocyte counts of less than 500/μL. Two of 6 with indeterminate QFT-G results had malignancies, and 1 of these had a terminal gastric cancer. Three of the 4 remaining patients (75%) had low serum Alb levels of 1.8, 2.0, and 2.0 g/dL, despite not having any particular underlying disease. Jones et al (27) reported that the severe tubercular infections were associated with a low volume of serum Alb and CD4 lymphocyte counts in a study that measured CD4 lymphocyte counts of HIV-negative patients. Serum Alb was found to significantly affect the QFT-G sensitivity in the multivariate analysis of the study of Jones et al. However, the effect was not as remarkable as that of the lymphocyte count. This finding suggested that not only malnutrition but also advanced tuberculosis was a factor for indeterminate results (27-29). In contrast, 1 patient had an indeterminate result, despite having a lymphocyte count of 1,640/μL. Although this patient was a 54-year-old male with no underlying disease, he had giant cavities in bilateral lung fields. In advanced tuberculosis with giant cavities, the disease state itself may control lymphocyte function, increasing the expected risk of false negative findings (3, 27, 30-32). Therefore, these factors may have influenced the indeterminate result.

In the 16 patients with negative results for both QFT-G and ELISPOT, 5 (31%) were currently receiving immunosuppressive therapy, and their median lymphocyte count was conspicuously low (616/μL, IQR: 201, 1,776). This result confirmed that the long-term administration of glucocorticoid decreased the T lymphocyte count (33, 34). In contrast, Matulis et al (35) reported that neither corticosteroids nor conventional DMARDs significantly affected IFN-γ responses, but the odds for a positive IFN-γ assay decreased in patients treated with TNFα inhibitors. In the 33 patients, immunosuppressive therapy subjects constituted a smaller proportion among the group with negative results for QFT-G and positive results for ELISPOT than among the group with negative results for both assays. Moreover, all QFT-G-positive patients were positive for ELISPOT. There were few immunocompromised hosts in these subjects.

Thus, this study has indicated that the sensitivity of 2 IGRAs, QFT-G and ELISPOT, has the tendency to correlate with the peripheral lymphocyte count. This is not contradictory to the study by Ariga et al, who also found that sensitivity of QFT-G was influenced by the peripheral lymphocyte count in HIV-negative patients (Ariga et al in preparation). However, in some cases, the results of IGRAs were negative, although lymphocyte counts were not low. In multivariate analysis, the lymphocyte counts and serum Alb significantly affected QFT-G sensitivity, while lymphocyte counts and immunosuppressive therapy affected ELISPOT sensitivity. Based on the above, lymphocyte count alone does not affect the sensitivity of IGRAs and the IFN-γ production ability of lymphocytes may be a contributing factor. The IFN-γ production ability of lymphocytes could be measured in the positive control, and thus future research is expected.

This study also indicates that for maximum sensitivity, ELISPOT is preferred to QFT-G. The difference of sensitivity between ELISPOT and QFT-G is based on the difference in the testing principle (3). A reliable method of detecting LTBI is required for implementing this therapy. Measures that could be taken to improve the performance of IGRAs include re-evaluation of the recommended cut-off (36) for each geographic region and exploration of alternative biomarkers for tuberculosis diagnosis.

Conclusion

The sensitivity of 2 IGRAs, QFT-G and ELIPSPOT, is partly dependent on peripheral lymphocyte counts. With low lymphocyte counts, the clinically acceptable sensitivity was better maintained with ELISPOT than QFT-G. Since the ELISPOT sensitivity is not affected by age, gender, and the nutritional state, ELISPOT is superior to QFT-G for detecting active tuberculosis in HIV-negative immunocompromised patients.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

The Value of Fiberoptic Bronchoscopy in Culture-Positive Pulmonary Tuberculosis Patients Whose Pre-Bronchoscopic Sputum Specimens were Negative both for Smear and PCR Analyses

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Abstract

Objective This study assessed the diagnostic rate of pulmonary tuberculosis (PTB) using fiberoptic bronchoscopy (FBS) in patients with suspected PTB, and negative pre-bronchoscopy smear and polymerase-chain reaction (PCR) in sputum.

Patients and Methods We retrospectively reviewed 201 culture-positive PTB patients that underwent FBS because both smear and PCR results in sputum were negative. The positive rates of smear for acid fast bacilli, PCR for *Mycobacterium tuberculosis*, the presence of granuloma in transbronchial biopsy (TBB), and culture of *M. tuberculosis* were analyzed. In addition, the radiographic features, contribution of FBS to rapid and/or definitive diagnosis of PTB, and drug susceptibility results of *M. tuberculosis* were also reviewed.

Results There were 136 males and 102 patients under the age of 40 years; non-cavitary (156 cases) and minimal disease (119 cases) on radiographs predominated. The positive rates of FBS were: 44% (smear), 62% (PCR), 61% (TBB), and 87% (culture). These rates increased in smear and PCR examinations when taken from wider spread shadows on radiographs. The combination of the various bronchoscopy samples increased the diagnostic rate to 92% when all examinations were combined. Positive culture results depended on FBS procedures in 80 cases. Twenty-one cases showed resistance to at least one of the major antituberculous agents.

Conclusion This analysis revealed high positive rates of PTB from bronchoscopy samples, providing rapid and definitive ability for PTB diagnosis, and details of drug susceptibility. Therefore, FBS is an important diagnostic procedure in patients with suspected PTB whose sputum specimens were negative both for smear and PCR analyses.

Key words: pulmonary tuberculosis, fiberoptic bronchoscopy, radiographic findings, rapid diagnosis, definitive diagnosis, drug susceptibility

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Introduction

Pulmonary tuberculosis (PTB) is one of the most prevalent infectious diseases in Japan. Although its incidence has decreased, it still affects a significant number of individuals. In 2007 the incidence was 19.8 per 100,000 people (1), which places Japan in the middle ranks of countries affected

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by this infectious disease. Many PTB cases were diagnosed and reported based only on clinical findings and/or chest radiographic findings without detection of acid-fast bacilli (AFB) in smears of sputum or gastric aspirate, although some cases later show AFB-positive culture results.

Several powerful laboratory-based diagnostic examinations, such as the polymerase-chain reaction (PCR) (2) and the second generation QuantiFeron-TB (QFT2G) (3), have recently been introduced. However, the former is a tool for rapid diagnosis, and QFT2G, a technique which has proved highly accurate in the detection of a *M. tuberculosis* infection, is influenced by several clinical conditions, such as immunosuppressive diseases, aging, and past infection of tuberculosis, and the presence of active tuberculosis cannot be diagnosed or excluded by the QFT2G result (4).

The procedure of fiberoptic bronchoscopy (FBS) is generally thought to be of importance in diagnosing pulmonary diseases (5). Since FBS has proved to be highly accurate in detecting *Mycobacterium tuberculosis*, the gold standard for the diagnosis of tuberculosis, FBS has been widely used to diagnose PTB in sputum smear-negative cases (6-11). FBS is also useful for the differential diagnosis and for the treatment of tuberculosis via the drug susceptibility test if *M. tuberculosis* can be obtained. However, the number of cases of smear, culture, PCR, and transbronchial biopsy (TBB) findings using FBS in previous Japanese reports is relatively small (6-8, 12-14). Furthermore, the usefulness of FBS in patients whose pre-bronchoscopy samples showed both AFB-smear and *M. tuberculosis*-PCR negative results has been uncertain.

Under the current Japanese law, hospitalization is recommended for patients with suspected infectious tuberculosis based on clinical judgment alone; a positive sputum smear result for AFB is not necessarily required. Therefore, it is very important to differentiate other diseases and obtain a rapid diagnosis of PTB in patients with suspected PTB in order to ensure their prompt hospitalization for treatment. Here, we assessed the diagnostic accuracy of FBS in patients with culture-positive PTB whose sputum smears for AFB and sputum PCR for *M. tuberculosis* were both negative when performing FBS.

Materials and Methods

When reviewing the usefulness of a procedure for diagnosing certain diseases in suspected cases, objectives must be clearly defined in advance, and the value of the test is usually evaluated by calculating the sensitivity, specificity, and positive predictive value, etc. This can be done by recording the number of true-positive findings, false-positive findings, true-negative findings, and false-negative findings in a 2×2 table, and then comparing the various incidences. However, if AFB is not detected in sputum samples, then PTB is often clinically diagnosed by chest radiographic findings, the presence of the epithelioid cell granuloma in a TBB, and more recently, by the positive results of the QFT2G examination alone, followed by empirical anti-PTB treatment while waiting for culture results. Furthermore, since cases of pulmonary non-tuberculous mycobacteriosis are included among the suspected cases of PTB, positive findings of epithelioid cell granuloma and sputum smear-positive for AFB could also be indicative of this non-tuberculous condition, thus making it difficult to develop an accurate protocol in a prospective study based on the 2×2 table as described above.

Therefore, in many studies investigating the usefulness of FBS for PTB diagnosis, objectives have been defined based on a final diagnosis of PTB (6-8, 10, 12-15). As in those studies, the current study focused on the ability of FBS to make a diagnosis of PTB in cases that were ultimately proven to be *M. tuberculosis*-culture positive.

A total of 4,769 culture-positive tuberculosis patients were admitted to this hospital in the 13 year period from 1996 to 2008. The medical records of 201 PTB patients who met the following criteria for inclusion in this study were retrospectively reviewed: 1) smear-negative for AFB on admission (one to three times in sputum, and zero to twice in gastric aspirate), 2) PCR-negative for *M. tuberculosis* on admission (once in sputum and zero to once in gastric aspirate), 3) FBS for making a diagnosis was performed before treatment for PTB, and 4) final diagnosis of PTB was based on the identification of *M. tuberculosis* cultured from at least one of the following samples: sputum and/or gastric aspirates on admission (pre-bronchoscopy samples), bronchial washing and/or aspirate (bronchoscopy samples), and post-bronchoscopy sputum samples. Since previous reports (6, 7) have shown post-bronchoscopy sputum examinations to be a reliable method for detecting *M. tuberculosis*, the examination of post-bronchoscopy sputum has now become a routine procedure, and in this study post-bronchoscopy sputum smear and culture data were automatically included if pre-bronchoscopy and bronchoscopy samples showed negative data. Cases with miliary tuberculosis and/or endobronchial tuberculosis were excluded, even if FBS was performed for the diagnosis of tuberculosis.

All FBS investigations performed by experienced physicians were done via the transoral or transnasal route under local anesthesia and sedation, and according to standard procedures: 1) complete inspection of the tracheobronchial trees including subsegmental bronchi and collection of a bronchial aspirate (BA) if bronchial secretions existed; 2) sampling of bronchial brushings (BB, once to three times) from the bronchial segments at which the lesion had been radiographically located; 3) TBB from the same segments; and 4) collection of a bronchial washing (BW) at the orifices of the same segment.

The evidence of a bronchoscopy positive sample was defined as follows: i) a positive sample from at least one among BA, BB, BW, and a mixture of BA and BW in smear examination for AFB; ii) a positive sample which is either among BA or BW, and a mixture of BA and BW in a PCR examination for *M. tuberculosis*; iii) the presence of

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Table 1. Baseline Demographics and Radiographic findings

Factors	Number of Patients (n=201)
Demographics	
Sex	
Male/female	136/65
Age	
~39 yrs (~29 yrs)	102 (51)
40~69 yrs	71
70 yrs~	28
Radiographic findings*	
Type	
II	45
III	156
Spread	
1	119
2	80
3	2

*: according to the classification of pulmonary tuberculosis designated by the Japanese Society for Tuberculosis (Gakkai Classification)[16]

epithelioid cell granuloma or AFB in TBB tissue; iv) a positive sample from at least one among BA, BW, and a mixture of BA and BW in culture examination for *M. tuberculosis*. When spontaneous sputum was not obtained, sputum was induced by either inhalation of a hypertonic, or normal saline, or a bronchodilator plus normal saline. However, the medical files showed that no distinction was made in clinical practice between spontaneous and induced sputum, and therefore these samples were grouped together into the category of pre-bronchoscopy sputum samples. Post-bronchoscopy sputum examination was performed once, after the FBS procedure in all 201 cases, either on the same day as the FBS or on the following day.

This study analyzed the rates of positive smear for AFB, PCR of *M. tuberculosis*, presence of epithelioid cell granuloma or AFB in TBB, culture of *M. tuberculosis* in bronchoscopy samples, culture of *M. tuberculosis* in pre-bronchoscopy samples, and smear for AFB and culture of *M. tuberculosis* in post-bronchoscopy samples. We also examined the drug susceptibility of *M. tuberculosis* identified by culture.

The findings were analyzed according to the classification of pulmonary tuberculosis designated by the Japanese Society for Tuberculosis (Gakkai Classification (16)) in order to consider how the radiographic findings influenced the diagnostic ability of FBS. The Gakkai classification consists of 3 Types and 3 Spreads on plain chest X-rays; Type I: extensively cavitary, Type II: non-extensively cavitary, Type III: non-cavitary, Spread 1: minimal disease, Spread 2: intermediate disease, Spread 3: extensive disease.

Drug susceptibility tests before November 2001 were performed by the absolute concentration method using 1% Ogawa medium; the standard proportional method using WELLPACK was adopted in December 2001. Beginning in February 2003, the cultured *M. tuberculosis* was subjected to the standard method only when the obtained *M. tuberculosis* showed resistance to at least one of the following: isoniazid (INH), rifampicin (RFP), streptomycin sulfate (SM), and ethambutol (EB), by using the Mycobacteria Growth Indicator Tube method (BACTEC MGIT 960). This change was introduced because of reports of discrepancies in the results of drug susceptibility of *M. tuberculosis* between the standard and the MGIT methods (17), and because several reports had indicated that BACTEC MGIT 960 showed a higher proportion of INH resistance than the standard method (18).

The χ^2 test or Fisher's exact test (if adequate) were used for the statistical analysis of the frequency of various factors, and differences were considered to be significant at the $p<0.05$ level.

Results

The baseline demographics and radiographic findings of the 201 patients (136 males, 65 females) are shown in Table 1. The majority of patients (102/201, 51%) were aged 39 or under; only 28 patients (14%) were 70 years or older despite the fact that this age group represents over 50% of tuberculosis patients in Japan. According to the radiographic findings, as based on the Gakkai classification, Type III (non-cavitary, 156 cases) and Spread 1 (minimal disease, 119 cases) accounted for the majority of cases, both of which are thought to be less frequently associated with a positive sputum smear result than the other categories of

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Table 2. Rate of Positive Cases Detected by the Various Diagnostic Procedures

Samples	Positive cases / examined cases
Bronchoscopy samples	
Smear (BB, BA, BW)	88/201 (44%)
PCR for *M. tuberculosis* (BW, BA)	107/173 (62%)
Pathologic findings (TBB)*	75/123 (61%)
Culture (BW, BA)†	175/201 (87%)
Pre-bronchoscopy samples**	
Culture†	121/201 (60%)

Bronchoscopy = fiberoptic bronchoscopy, BB: bronchial brushing, BA: bronchial aspirate, BW: bronchial washing, PCR: polymerase-chain reaction, TBB: transbronchial lung biopsy, *: presence of epithelioid cell granulomas or acid-fast bacilli, **: sputum and/or gastric aspirate, †: The culture results were determined a few weeks after performing fiberoptic bronchoscopy.

Table 3. Relationship between the Procedures and Radiographic Findings of Pulmonary Tuberculosis

	Positive cases / examined cases			
	Types*		Spreads*	
Samples	Type II (n=45)	Type III (n=156)	Spread 1 (n=119)	Spread 2 (n=80)
Bronchoscopy samples				
Smear (BB, BA, BW)	22/45 (49%)	66/156 (42%)	41/119 (34%)†	47/80 (59%)†
PCR for *M.tuberculosis*	25/37 (68%)	82/136 (60%)	54/102 (53%)‡	52/69 (75%)‡
Culture (BW, BA)	37/45 (82%)	138/156 (88%)	105/119 (88%)	69/80 (86%)
Pathologic findings (TBB)**	22/29 (76%)	53/94 (56%)	44/71 (62%)	30/50 (60%)
Pre-bronchoscopy samples***				
Culture	30/45 (67%)	91/156 (58%)	69/119 (58%)	51/80 (64%)

Bronchoscopy = fiberoptic bronchoscopy

BB: bronchial brushing, BA: bronchial aspirate, BW: bronchial washing, PCR: polymerase-chain reaction, TBB: transbronchial lung biopsy,

*: according to the classification of pulmonary tuberculosis designated by the Japanese Society for Tuberculosis (Gakkai Classification)[16],

: presence of epithelioid cell granulomas or acid-fast bacilli, *: sputum and/or gastric aspirate

†: $p<0.001$, ‡: $p<0.005$

Types and Spreads. The percentage of positive cases from the FBS and pre-bronchoscopy samples are summarized in Table 2. FBS provided a positive-smear in 44% (88/201 cases) of the 201 patients who were negative for smear and PCR in their pre-bronchoscopy samples, and a positive-PCR in 62% (107/173 cases). One to four TBB specimens were obtained, and the positive rate reached 61% (75/123 cases). Although there are obvious limitations in the statistical comparison of the culture results of pre-bronchoscopy and bronchoscopy samples, the culture-positive rate in the bronchoscopy samples was high (87%, 175/201 cases) in comparison to the culture-positive rate in the pre-bronchoscopy samples (60%, 121/201 cases), suggesting the additional utility of FBS for detecting *M. tuberculosis* in patients with suspected PTB who have no bacterial evidence of PTB.

Table 3 shows the relationship between the original baseline radiographic features and the positive rates detected with the various procedures. These results indicated that, with TBB, there was a tendency for a higher positive rate with cavitary (Type II) cases in comparison to non-cavitary (Type III) cases, although this did not reach statistical significance. However, intermediate disease (Spread 2) cases showed a significantly higher positive rate in smear ($p<0.001$) and in PCR ($p<0.005$) examinations of the bronchoscopy samples in comparison to minimal disease (Spread 1) cases, although there were no significant differences in the positive rates between Spread 1 and 2 based on culture or TBB of bronchoscopy samples. There was no correlation between baseline demographics and radiographic findings or with the positive rates of the various diagnostics procedures.

As shown in Table 4, the step-wise combination of results from the various examinations increases the detection rate of positive cases from 44%, based on a smear in bronchoscopy sample alone, to 92% (152/166 cases) when the results of all bronchoscopy samples and post-bronchoscopy sputum samples were combined. This should translate into the

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Table 4. Rapid Diagnostic Ability for Pulmonary Tuberculosis according to the Cumulative Combination of Data from the Various Bronchoscopic Examinations

Combination of examinations	Positive cases/ examined cases
(a) smear in bronchoscopy samples	88/201 (44%)
(a) smear in bronchoscopy samples or (b) smear in post-bronchoscopy sputum samples	94/201 (47%)
(a) smear in bronchoscopy samples or (b) smear in post-bronchoscopy sputum samples or (c) PCR for *M. tuberculosis* in fiberoptic bronchoscopy samples	137/186 (74%)
(a) smear in bronchoscopy samples or (b) smear in post-bronchoscopy sputum samples or (c) PCR for *M. tuberculosis* in bronchoscopy samples or (d) pathologic findings*	152/166 (92%)

Bronchoscopy = fiberoptic bronchoscopy

PCR: polymerase-chain reaction, *: presence of epithelioid cell granulomas or acid-fast bacilli

Table 5. Drug Susceptibility Results of Culture-identified *M. tuberculosis*

Sensitivity	Bronchoscopy group (n=80)	Pre-bronchoscopy group (n=121)	Total (n=201)
All sensitive	72	108	180
RFP resistance	0	3	3
INH resistance	1	2	3
EB resistance	1	0	1
SM resistance	5	6	11
INH, SM resistance	1	1	2
INH, RFP resistance	0	1	1

Bronchoscopy = fiberoptic bronchoscopy

RFP: rifampicin, INH: isoniazid, EB: ethambutol, SM: streptomycin sulfate

timely start of PTB treatment in PTB-suspected patients. The definitive diagnostic ability of bronchoscopy for pulmonary tuberculosis is shown in Fig. 1. Cultures positive for *M. tuberculosis* were obtained in 40% of cases (80/201 cases) using bronchoscopy samples and post-bronchoscopy sputum samples, as opposed to pre-bronchoscopy samples. Of the 80 patients whose PTB diagnosis depended on FBS procedures, 51 were male (64%), 47 were under 40 years of age (59 %), 65 cases manifested non-cavitary disease (Type III, 81%), and 50 cases manifested minimal disease (Spread 1, 63%). There were no significant differences in the positive rates of the above factors between the 80 bronchoscopy-proven PTB patients and the remaining 121 patients who were subsequently diagnosed with PTB from a positive culture result of a pre-bronchoscopy sample, even if FBS had not been performed, but the radiographic evidence of bronchoscopy-proven PTB patients tended to show non-cavitary and minimal disease.

Finally, the drug susceptibility of the cultured *M. tuberculosis* (Table 5) was reviewed. The majority of cases (180/201, 90%) were susceptible to all four major anti-tuberculous drugs, but the remaining 21 cases (10%) showed resistance to at least one of the anti-tuberculous drugs, for example, 13 cases were resistant to SM (10 μg/mL), 6 to INH (0.2 μg/mL), 4 to RFP (40 μg/mL), and 1 to EB (2.5 μg/mL), either alone or in combination with other drugs. No significant differences were observed in drug susceptibility between the bronchoscopy-proven PTB patients and the remaining PTB patients.

This hospital is one of the selected hospitals for tuberculosis treatment. This FBS laboratory has been operating under depressurized ventilation conditions with high-efficiency filters since 1999; and all staff performing FBS procedures are required to wear an N95 mask. There have been no cases of tuberculosis, including latent tuberculosis, in the medical staff involved with FBS examinations. Seven out of

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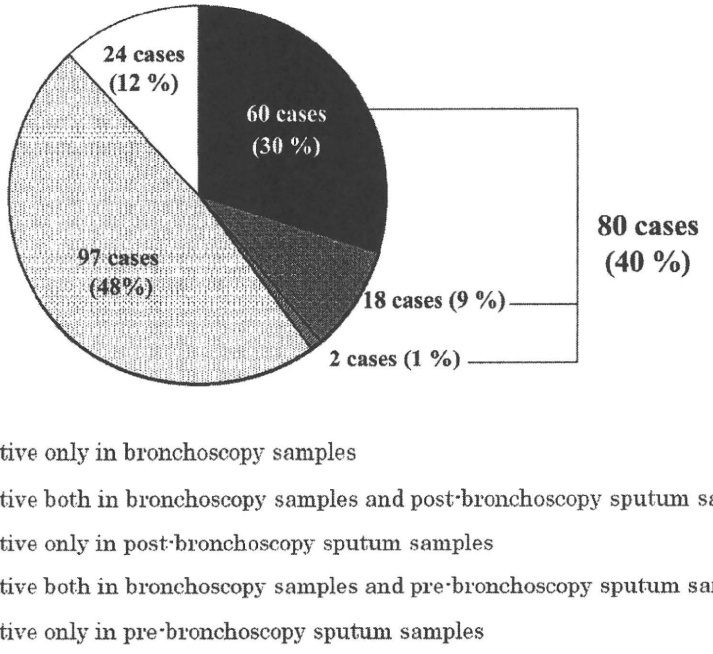

Figure 1. Definitive diagnostic ability of bronchoscopy for pulmonary tuberculosis. Relationship between the samples and *M. tuberculosis* culture-positive cases.

the 201 (3.5%) patients had pneumothorax, with 4 out of the 7 requiring tube drainage for this complication. However, no cases required treatment except for the use of intravenous styptic measures to cope with endobronchial hemorrhage at the time of the FBS procedure, and no other serious complications were reported.

Discussion

Kohno (6) reported in Japan in 1990 that, in a comparison of 91 BA and BW samples obtained via FBS, the smear-positive rates were 20.9% in BA and 23.9% in BW, and culture-positive rates were 58.2% in BA and 84.8% in BW. This report also demonstrated that TBB showed positive findings in 25 of 33 cases (75.8%), which led the authors to conclude that BW was superior to BA for the definitive diagnosis of PTB and that FBS was useful for obtaining a rapid PTB diagnosis. Subsequently, Kurashima and Takano (7) also indicated that BW was superior to BA for PTB diagnosis, and Kikuchi et al (8), based on the analysis of 50 cases using FBS, highlighted the usefulness of this procedure in a rapid (30%) and definitive (39%) PTB diagnosis. Outside Japan, the usefulness of smear and/or culture examinations of bronchoalveolar lavage fluid (BALF) obtained by bronchoscopy in patients with suspected PTB, whose sputum smear results were negative, has been shown in a few small case studies (9-11) (n=20-40). Baughman et al (19) also indicated the superiority of smears from BAL in comparison to sputum in detecting AFB (68%, 34/50 cases vs. 13%, 6/47 cases) and in obtaining cultures positive for *M. tuberculosis* (92%, 46/50 cases vs. 51%, 24/47 cases).

The use of PCR examinations for *M. tuberculosis* detection was introduced in the 1990s for the diagnosis of tuberculosis, but the sensitivity of PCR in smear-negative samples proved to be below 50%, and therefore, the 1997 guidelines of the American Thoracic Society (ATS) proposed that PCR examination should be limited to smear-positive samples (20). However, Wong et al (21) described that 105 out of 108 sputum smear-negative PTB cases were positive for *M. tuberculosis* based on PCR results from BA samples. Recently, Tueller et al (15) indicated that a PCR inspection using the FBS procedure was useful for the diagnosis of tuberculosis patients who had negative smear results in sputum samples, because PCR in BAL samples showed positive results in 93 of 120 (78%) cases that ultimately proved to be culture-positive for *M. tuberculosis*. Several Japanese reports using a small number of cases (n=34-82) have also indicated the usefulness of PCR for the detection of *M. tuberculosis* in BW (12-14). The present study established, in a relatively large sample size, high positive rates obtained in the bronchoscopy samples in patients who were culture positive, but who were negative for both their sputum smear and PCR, and has helped to confirm the validity of using FBS for PTB diagnosis.

To date, there have been few studies discussing the relationship between radiographic characteristics of PTB and positive rates of bronchoscopy samples. Kikuchi et al (8) discussed that FBS was useful for improving PTB diagnosis in cases with minimal disease, and Takahashi et al (14) indicated that the PTB diagnostic rate by FBS was higher in infiltrative shadow cases than in nodular shadow cases. The present study, for the first time, analyzed the association between radiographic features and positive rates of PTB samples in detail. The results showed that the presence or ab-

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sence of cavitary shadows did not affect the positive rates of the bronchoscopy samples, while the rates of smears that were positive for AFB and PCR positive for *M. tuberculosis* were higher in intermediate disease cases than in minimal disease cases, although there were no significant differences between those of TBB and culture. These results suggest that there is a much stronger association between the precision of FBS sampling from the PTB lesions and obtaining a definitive diagnosis of PTB than there is between the characteristics of PTB shadows on radiographs and a diagnosis; nevertheless a rapid diagnosis was more easily and more frequently obtained from shadows with a larger spread on radiographs.

Among the benefits of FBS in PTB diagnosis, is that the combination of variously derived bronchoscopy sample data such as smear and PCR of BALF (15), smear and PCR of BW and TBB (14) can increase the ability to obtain a rapid diagnosis. The present study demonstrated that the positive diagnostic rates increased as greater numbers of bronchoscopy samples were combined. The positive rate reached 92% when smear, PCR, and TBB of bronchoscopy samples were all combined with post-bronchoscopy sputum smear, indicating the value of the combined use of bronchoscopy samples in achieving a rapid PTB diagnosis. To arrive at a definitive diagnosis of PTB by obtaining cultures positive for *M. tuberculosis*, FBS has previously been considered to be significant (6-11), and recently Dickson et al (22) also confirmed that BALF culture is superior to culture of gastric aspirate for obtaining positive culture results. In this study, we obtained positive cultures for *M. tuberculosis* in 175 of the current 201 cases (87%), furthermore, 80 out of the 201 (40%) cases were cases where *M. tuberculosis* would not have been obtained if FBS had not been performed. There were no significant differences in the radiographic features between the 80 bronchoscopy-proven PTB cases and the remaining 121 cases in which positive cultures of *M. tuberculosis* would have been obtained even if FBS had not been performed. These results indicate that it is not possible to predict the culture outcome of FBS using the radiographic findings.

It is possible to ascertain precisely which drugs to select as treatment for PTB by obtaining cultures of *M. tuberculosis* and conducting a drug susceptibility test. However, this aspect has not been addressed in any of the previous reports on the FBS examination. Yoshiyama et al (23) reported that about half of the multidrug-resistant tuberculosis cases have acquired resistance and that understanding drug susceptibility of cultured *M. tuberculosis* is very important in measuring this phenomenon. Therefore, the implementation of the drug susceptibility test is regarded as important in the current standard treatment criteria for tuberculosis (24). Drug-resistance to INH, RFP, EB, and/or SM in this study was present in 8 out of 80 cases (10%) in which PTB was diagnosed only by FBS. The use of a drug susceptibility test on cultured *M. tuberculosis* obtained by FBS procedures is thought to be valuable for securing the success of PTB treatment in a way that cannot be obtained by QFT2G examination.

Problems of nosocomial infection and complications are often cited as the disadvantages of FBS procedures; no cases of tuberculosis (including latent tuberculosis) have occurred among the medical staff concerned with the FBS examinations in this laboratory. The ATS also suggests that FBS should be performed with appropriate infection control precautions with BAL and/or TBB for patients in whom a diagnosis of tuberculosis has not been established from sputum (25). We consider that the benefits of current FBS procedures outweigh the risks and its use should therefore not be avoided due to any fears of nosocomial infection.

The findings of the present study concluded that FBS is an important procedure to obtain a diagnosis for patients with suspected PTB whose sputum smear and PCR results were both negative. This conclusion is based on the ability of FBS to arrive at a rapid and definitive diagnosis, coupled with the opportunity it provides to test for drug susceptibility. Comparisons between the relative abilities of FBS and QFT-2G in tuberculosis diagnosis, the assessment of the rapidity of diagnosis achievable by combining the data from these two modalities, and also the usefulness of transcription-reverse transcription concerted reaction (TRC) examinations (26) which have been recently introduced in place of PCR examinations to evaluate bronchoscopy samples, should therefore be the focus of future studies.

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結核性胸膜炎に対する胸腔ドレーン留置後に発症した胸壁冷膿瘍の1例

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要旨：症例は56歳男性。3カ月前に左結核性胸膜炎の診断を受けて，INH，RFP，EB，PZAによる抗結核薬の開始および2週間の胸腔ドレーン留置が行われた。約2週間前より胸腔ドレーン刺入部に一致して，胸壁の皮下腫瘤を自覚するようになり徐々に増大した。当院入院時には，直径10 cm程度の熱感を伴う硬い皮下腫瘤として触知した。胸部造影CTでは，左胸腔内膿瘍およびその外側の皮下膿瘍があり，辺縁が造影されるrim enhancementを認めた。胸部MRIでは，肋骨の破壊像はなく，胸腔内膿瘍から皮下に交通するダンベル型の膿瘍を認めた。皮下腫瘤を穿刺吸引したところ，抗酸菌集菌塗抹2＋，抗酸菌培養陽性，結核菌DNA-PCR陽性であり，結核性の胸壁冷膿瘍と診断した。すなわち，胸腔内膿瘍が胸腔ドレーン刺入部位から流注した胸壁皮下膿瘍と判断した。抗結核薬の継続とともに，頻回の穿刺吸引を繰り返したところ，熱感は徐々に消失し腫瘤も縮小傾向となった。穿刺液の抗酸菌塗抹および培養も陰性化し，画像上も膿瘍病変の縮小を認めた。抗結核薬終了後の現在も，再燃せず経過は良好である。

キーワーズ：結核性胸膜炎，胸囲結核，胸壁冷膿瘍，皮下膿瘍，胸腔ドレナージ

はじめに

胸壁に生じる結核性病変は肺外結核の中でも少なく，中でも医原性に生じた例はきわめて稀である。結核性胸膜炎に対する胸腔ドレーン留置後に発症した胸壁冷膿瘍の症例を経験したので，文献的考察を加え報告する。

症　例

症　例：56歳，男性。
主　訴：左側胸部皮下腫瘤。
既往歴：多発性嚢胞腎。肺結核の既往なし。
家族歴：特記すべき事項なし。
喫　煙：40本/日（20～31歳）。
飲　酒：日本酒3合/日。
現病歴：2008年6月に労作時の呼吸困難で近医を受診し，胸部単純エックス線写真にて中等量の左胸水を認めた。胸部CTでは被包化されていない左胸水を認め，肺野には異常を認めなかった。局所麻酔下胸腔鏡による胸膜生検で乾酪性肉芽腫を認め，胸水は淡黄色で滲出性，結核菌DNA-PCR陽性であったことから結核性胸膜炎と診断された。6月28日よりイソニアジド（INH）400 mg，リファンピシン（RFP）450 mg，エタンブトール（EB）750 mg，ピラジナミド（PZA）1.5 gが開始され，胸腔ドレーンが2週間留置された。肝機能障害のため7月12日からPZAが中止となり，胸腔ドレーン抜去後も胸水の再貯留を認めず7月30日に退院した。9月初旬頃より，左側胸部の胸腔ドレーン刺入部に徐々に増大する腫瘤を自覚するようになり，9月18日に同院を受診した。胸部造影CT写真にて結核性の胸腔内膿瘍および皮下膿瘍が疑われ，同日当院へ紹介入院となった。

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入院時現症：脈拍80/分整，血圧116/60 mmHg，呼吸数18/分，体温37.2℃，酸素飽和度98%（room air），左側胸部に胸腔ドレーンの刺入瘢痕があり，その部位を中心に10 cm大の腫瘤を認めた。可動性不良で，弾性硬で熱感を伴っていた。呼吸音および心音に異常なし。

入院時検査成績（Table）：血算では正球性の貧血を認め，生化学では軽度腎機能低下を認めた。免疫ではCRPの上昇があり，腫瘍マーカーではごく軽度の可溶性インターロイキン2受容体（sIL2-R）の上昇を認めた。入院時の喀痰・尿では抗酸菌塗抹・培養陰性，結核菌DNA-PCR陰性，抗酸菌培養陰性であった。胸部単純エックス線写真では，左肺の軽度の容量低下があり，左肋骨横隔膜角の鈍化とその周囲の浸潤影を認め，外側に軟部組織の肥厚を認めた（Fig. 1）。入院時の胸部造影CTでは，先天性の肝および腎に多発する嚢胞以外に，左背側の胸膜に石灰化を伴わない肥厚を認め，そのやや背側には辺縁が造影される卵円形の限局性の低吸収域を2カ所（40×20 mm，30×10 mm）認めた。そのうち1カ所（40×20 mm）の近傍には皮下膿瘍がみられた（Fig. 2）。入院10日後のMRIでは，T1W1で均一な低信号，T2W1にて内部に低信号を含む高信号を示す皮下膿瘍が見られ，胸腔内の膿瘍と連続性がありダンベル型を呈していた（Fig. 3a）。前額断でも，胸腔内膿瘍と皮下膿瘍との連続性を認めた（Fig. 3b）。画像上，肋骨の融解および破壊像は認めなかった。また，このMRI画像を10日前に撮影した入院時CT画像と比較すると連続する胸腔内膿瘍の一つが縮小するとともに，皮下膿瘍が増大している所見であった。

Table Laboratory data on admission

Hematology		Chemistry		Acid fast test	
WBC	9000 /μl	Alb	3.8 g/dl	Sputum	
Neu	83.2 %	AST	18 IU/l	smear	(−)
Mon	4.0 %	ALT	11 IU/l	culture	(−)
Lym	12.4 %	ALP	57 IU/l	Urine	
Eos	0.3 %	LDH	137 IU/l	smear	(−)
Hb	9.2 g/dl	BUN	17.7 mg/dl	culture	(−)
MCV	89.1 μ^3	CRE	1.03 mg/dl	Subcutaneous abscess	
PLT	47.4×10^4 /μl	Na	138 mEq/l	smear	(+)
		K	4.3 mEq/l	culture	(+)
Serology		HbA1c	5.6 %		
CRP	6.66 mg/dl			QFT®TB-2G	(+)
ESR	91 mm/hr	Tumor marker			
HBs-Ag	(−)	CEA	0.7 ng/ml		
HCV-Ab	(−)	SCC	0.9 ng/ml		
HIV-Ab	(−)	NSE	5.8 ng/ml		
		sIL-2R	1330 U/ml		

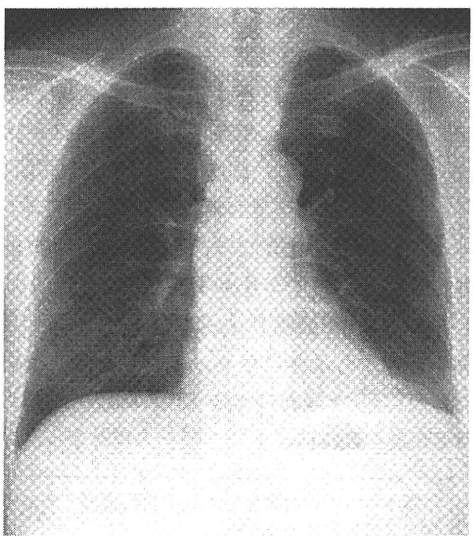

Fig. 1 Chest X-ray on admission (18 Sep. 2008)

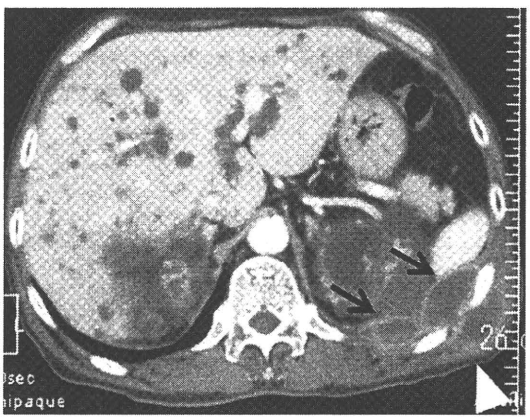

Fig. 2 Enhanced chest CT on admission showed empyema of the left thoracic space and subcutaneous localized abscess with rim enhancement. (18 Sep. 2008)
Encapsulated empyema (arrow)
Subcutaneous abscess (arrow-heads)

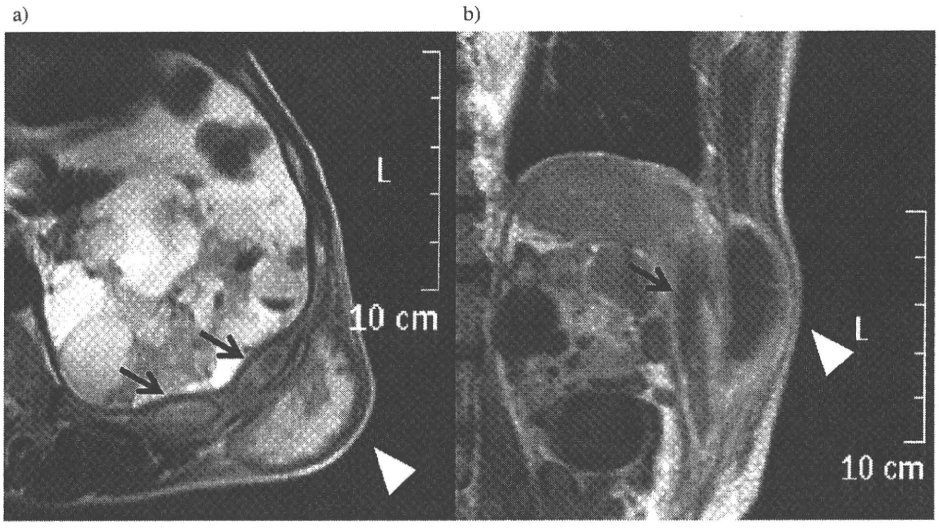

Fig. 3 Chest MRI 10 days after admission showed a dumbbell-shaped abscess through the chest wall communicating with an empyema in the left thoracic space. (28 Sep. 2008)
a) Cross-section T2W1 b) Frontal-section Gd enhanced T1W1
Encapsulated empyema (arrow) Subcutaneous abscess (arrow-heads)

臨床経過：9月19日に左側胸壁の皮下腫瘤を穿刺したところ，きわめて少量の血性検体を採取した。穿刺液の抗酸菌塗抹は陽性，結核菌DNA-PCR陽性，培養でも陽性を確認した。その他，有意な一般細菌や悪性細胞は検出しなかった。腫瘤は胸腔ドレーン刺入部の瘢痕に一致しており，CTやMRI上胸腔内膿瘍から連続した皮下膿瘍と判断した。穿刺液からの結核菌は以下の薬剤に耐性がないことを確認し，INH，RFP，EBに加え，ストレプトマイシン（SM）0.75 g×3/週を追加投与した。入院中，頻回の穿刺排膿を行ったところ，腫瘤は徐々に軟化・縮小し熱感も消失した。10月初旬頃には白濁した膿汁を1回につき30 cc程度穿刺吸引可能となった。10月中旬には解熱し炎症反応も陰性化した。11月には腫瘤は徐々に縮小傾向となった。穿刺液の抗酸菌培養陽性までの日数は穿刺ごとに徐々に延長し，塗抹も11月中旬には陰性化した。今後は抗結核薬を継続し，必要に応じて穿刺排膿を行う方針とし11月20日に退院した。外来通院中に穿刺を要するような腫瘤の緊満はなく，2009年6月20日に抗結核薬は終了した。その後再燃はなく，抗結核薬終了後約6カ月経過した時点でのMRIでは，皮下膿瘍およびそれに連続していた胸腔内膿瘍は明らかに縮小していた（Fig. 4）。また，病巣は臀部や背部などに拡大している所見はなかった。

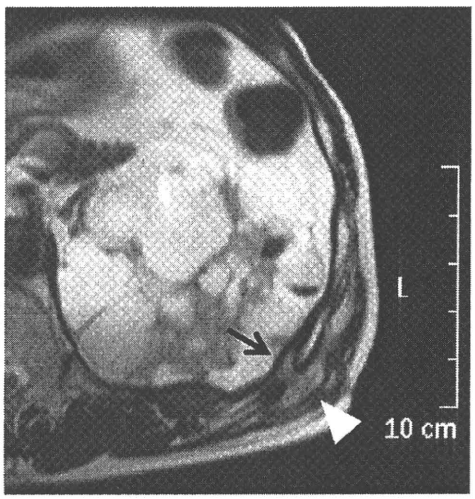

Fig. 4 Chest MRI 6 months after completion of chemotherapy; cross-section T2W1 (7 Jan. 2010)
Encapsulated empyema (arrow)
Subcutaneous abscess (arrow-heads)

考　察

結核性胸膜炎に対する胸腔ドレーン留置後に発症した胸壁冷膿瘍の1例を報告した。胸壁に生じる結核病変の機序としては，①肋骨，胸骨および胸椎カリエス，②胸腔内病巣から結核菌が波及，③血行性に胸壁軟部組織に結核菌が侵入したもの，と大きく3つに分類できる。①は，骨，骨髄に血行性に結核菌が侵入し，そこで骨破壊性結核性病巣をつくり，その後周辺軟部組織にも病変が拡大するものであり，②③は骨を介することなく直接軟部組織に病変を形成するものである。諸家の報告では，②③を胸囲結核と称することがある[1)2)]。

②はさらにその機序が3通りに報告されている。第一

に，結核性胸膜炎による胸膜の癒着，肥厚により，リンパ管が新生し胸壁のリンパ管網と吻合し胸腔内の結核菌がリンパ流に乗り，胸壁軟部組織に到達するもの[3]，第二に，結核性胸膜炎後に限局性膿瘍を併発し，胸壁軟部組織に穿破するもの[1)4)]，第三に，結核性胸膜炎に対して胸腔穿刺を行ったことで医原性に胸腔内の結核菌が胸壁の軟部組織内に播種され膿瘍化したもの[5)6)]である。これらは，手術検体や造影検査で瘻孔が確認できれば区別しやすいが，厳密には困難な場合が多い。

いずれにしても胸壁の結核病変は稀であり，中でも結核性胸膜炎に対して胸腔穿刺を行ったことで生じる医原性のものは調査したかぎり報告は2例のみであった[5)6)]。実診療ではそれ以上に生じている可能性も推測されるが，報告された症例の特徴は以下であった。Guestらは，結核性胸膜炎の診断にCope針を用いた胸膜生検を行った10カ月後に，生検部位に一致して皮下腫瘤を認め，胸腔から皮下膿瘍まで連続するダンベル型の膿瘍を形成していたことを報告した[6)]。この症例では，胸腔内膿瘍を含め連続する皮下膿瘍を全摘出し治癒している。胸腔と皮下膿瘍の交通は摘出標本で確認された。野中らは，原因不明の胸水に胸腔ドレナージを施行された2年後に，ドレーン刺入部位に一致して結核性の皮下膿瘍を形成した症例を報告していた[5)]。この症例では，胸腔内に限局性の胸腔内膿瘍を認めていたが，手術では皮下膿瘍と胸腔内膿瘍との連続性はみられず，胸腔穿刺による胸水採取時の胸壁播種による膿瘍形成と判断され，開胸剝皮術は行わず抗結核薬を開始したことで経過は良好としている。これらの報告を踏まえると，皮下膿瘍が胸腔内膿瘍と連続しているか否かによって，医原性と考えられる皮下膿瘍は以下の二つの機序が推測できる。すなわち，胸腔穿刺時に軟部組織に結核菌が播種されたことが成因なのか，もしくは結核性胸膜炎後の限局性の胸腔内膿瘍が何らかの過程で膨張する際，線維化した被膜が強固なため胸腔内での増大を許さず，壁側胸膜と癒着した部位でかつドレーン刺入部という構造的に脆弱な部分を介して皮下に流注したことが成因なのかといった機序である。臨床上は，皮下膿瘍が胸腔内膿瘍と連続している場合，胸腔内膿瘍が排膿源と考えられるために手術適応の検討を推奨する報告が散見される[1)5)7)~9)]。

本症例では画像所見から胸腔内の被包化された胸腔内膿瘍と皮下膿瘍の連続性およびその流注が強く疑われたため，後者の機序が考えられた。繰り返す穿刺吸引と抗結核薬のみで皮下腫瘤および連続する膿胸が縮小した。穿刺液からも抗酸菌は消失し，抗結核薬終了後も再燃がないことから，ほぼ治癒した状態と判断できる。春名らは，皮下膿瘍と胸腔内膿瘍との連続性についての記載はないものの，結核性胸膜炎後の胸郭結核10例の検討で，外科的治療を行わずとも内科的治療で経過が良好な症例があったことを報告し，必ずしも外科的治療を行う必要はないことを述べている[4)]。その他にも，結核性胸膜炎と穿通性皮下膿瘍を同時発症した症例で，抗結核薬と穿刺吸引で改善した報告[10)]や，詳細な背景の記載がないものの3例の結核性皮下膿瘍に対して，抗結核薬と繰り返す穿刺吸引のみで改善したことが報告されている[11)]。

以上のように，胸壁冷膿瘍においては，常に外科適応を念頭に入れる必要はあるが，患者の状態によってまずは内科的治療で経過を見ても管理できる可能性が考えられる。ただし，薬剤耐性菌もしくは抗結核薬の副作用で十分な化学療法が困難な場合や内科的治療において増悪または皮下膿瘍穿刺部位が自壊するようであれば，早めの手術適応も考慮する必要がある。また，結核性胸膜炎の初期治療における胸水ドレナージの可否については未だ議論されている[12)~15)]。胸腔と皮下との連続性を容易にする危険性があるドレーン留置や胸腔鏡といった手技は，刺入口径やその留置期間などを含め十分な注意を払う必要がある。ただし，先述のように胸壁冷膿瘍はドレナージの既往の有無にかかわらず発症しうる。したがって，特に結核性胸膜炎後の胸壁腫瘤の鑑別として常に本疾患を考慮することは重要と考える。

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Case Report

A CASE OF COLD ABSCESS OF THE CHEST WALL DUE TO THORACIC DRAINAGE FOR TUBERCULOUS PLEURITIS

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Abstract A 56-year-old man underwent thoracic drainage for two weeks for tuberculous pleuritis. He was put on anti-tuberculosis chemotherapy with INH (400 mg), RFP (450 mg), and EB (750 mg). Two months later, he developed an elastic hard subcutaneous mass in the area of the previous thoracic drainage. The mass was 10 cm in diameter, warm, reddish and painful. Chest computed tomography (CT) revealed localized and encapsulated empyema in the left thoracic space and a subcutaneous abscess with rim enhancement in the left lateral chest wall. Magnetic resonance imaging (MRI) demonstrated a dumbbell abscess in the subcutaneous tissue communicating with the empyema through the chest wall. A needle aspiration of the subcutaneous abscess had acid-fast bacilli smears of 2+ and tested positive by polymerase chain reaction (PCR) for *Mycobacterium tuberculosis*. Thus, he was diagnosed with a cold abscess of the chest, with the empyema in the thoracic space draining into the chest wall through the cut for artificial drainage. Continuation of the anti-tuberculosis treatment and the drainage of the empyema with repeated aspiration reduced the subcutaneous mass, and the clinical and radiological course was favorable. Both the smear and culture for acid-fast test became negative. After completion of chemotherapy, there has been no disease recurrence.

Key words: Tuberculous pleuritis, Chest wall tuberculosis, Cold abscess of the chest wall, Subcutaneous abscess, Chest drainage

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高齢者結核の臨床的検討

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要旨：〔目的〕高齢者結核の臨床的実態を明らかにし，その対応への改善策を検討する。〔対象と方法〕対象は2008年1月から12月に当院結核病棟で入院治療した活動性結核患者414名である。年齢により，64歳以下（非高齢者群），65～74歳（前期高齢者群），75歳以上（後期高齢者群）の3群に分けて比較検討した。比較項目は，入院時のPS，アルブミン値，合併症，有症状受診の場合の症状，喀痰塗抹陽性率，空洞病変の有無，開始した治療内容，副作用の有無，抗結核薬の中断・変更および予後である。〔結果〕非高齢者は187名，前期高齢者群は74名，後期高齢者群は153名で，高齢者は非高齢者と比較して，呼吸器症状が乏しく，入院時PSが不良で，低アルブミン血症（3.0 mg/dl未満）が多い傾向である。治療が困難で，死亡退院が多かった。QFT陽性率は後期高齢者（75歳以上）では他の群よりも，陽性率が低く陰性率が高い結果であった。〔考察〕高齢者結核は症状，画像所見が非特異的で診断が遅れやすく，治療が困難な症例が少なくないため，予後が不良となりやすい。早期に発見，早期治療開始することが重要と思われる。また栄養やリハビリテーションを早期から併用してサポートしてゆくことが望まれる。

キーワーズ：高齢者結核，加齢，Performance status，低アルブミン血症，QFT陽性率

はじめに

2008年，日本の新登録結核患者は24,760人，罹患率人口10万対19.4と減少傾向を保ち，低蔓延に向かっている。日本の結核の特徴の一つは高齢者がその半数以上を占めることである[1)~3)]。医療現場では，高齢者に標準治療を完遂することは困難なことが多く[4)]，無理な導入はかえって予後を悪くし，Activities of daily living（ADL）やQuality of life（QOL）を下げて困窮する結果となりうる。高齢者結核の入院の実態を把握し予後を見通してより良い医療を実現することを目的として，2008年に当院へ入院した高齢者結核患者の検討を行った。

対象と方法

2008年1月から12月に当院結核病棟で入院治療した活動性結核患者414名（臨床診断を含む）を，年齢により，64歳以下（非高齢者群），65～74歳（前期高齢者群），75歳以上（後期高齢者群）の3群に分けて比較した。検討項目は，症状，喀痰塗抹陽性率，空洞病変の有無，入院時のPerformance status（PS），アルブミン値，開始時の治療内容，副作用の有無，投薬中断や変更の有無，死亡退院症例などについて，結核患者データベースおよび診療録を用いて後ろ向きに検討した。統計解析にはχ^2検定を用いて，$p<0.05$にて有意差ありと判定した。

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結　果

全活動性結核414名の年齢分布は（Fig.）に示した。65歳以上は227人（男性143，女性84）で全体の54.8%を占めていた。A）非高齢者群：187名（平均年齢45.6±13.0歳），B）前期高齢者群：74名（平均年齢69.8±2.79歳），C）後期高齢者群：153名（平均年齢84.4±6.04歳）の結果は，以下%としてA），B），C）群の順に表示する。

入院時患者の状況をTable 1に示した。PS 3以上の患者は，各群の13.4%，24.3%，54.2%，アルブミン値3.0 g/dl未満は23.0%，40.5%，52.3%と高齢群ほど高くなっており，悪性疾患，糖尿病，ステロイドや免疫抑制剤を投与中，血管障害，腎不全などの重要な合併症を有さない患者の割合は59.9%，21.6%，20.9%であった。

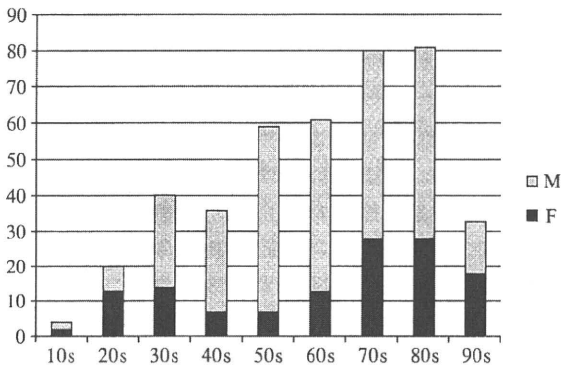

Fig. Age distribution of 414 active TB patients: Elderly patients (≧65 years) occupied 54.8% of all the in-patients with TB.

医療機関受診時の症状についてはTable 2に示した。咳，痰など呼吸器症状を有した者は48.7%，33.8%，31.4%，発熱，体重減少，ADLの低下などの全身症状を訴えていた人は17.1%，20.3%，38.6%と，高齢者群では呼吸器症状はむしろ少なく，結核に非特異的な症状で発症し医療機関を受診していることがわかった。健康診断で発見されることは高齢者では少なかった。喀痰塗抹陽性率は，74.9%，75.7%，77.1%で差はなかった（Table 3）。空洞病変を有する症例は，56.1%，33.8%，30.1%と高齢者では少ない傾向であった（Table 3）。結核治療についてはTable 4に示す。PZAを含む標準治療は79.1%，55.4%，19.6%と高齢者で低く，治療中の抗結核薬の副作用の出現は，35.3%，39.2%，24.8%で後期高齢者ではむしろ少ない傾向であった。しかし治療薬の変更や中断は20.3%，35.1%，27.5%と副作用の出現頻度とは並行していない。死亡退院は，4.3%，13.5%，35.3%と明らかに高齢者に偏在していた。

414名のうちで入院2週間以内にクォンティフェロン® TB-2G（以下QFT）を実施し，なんらかの検体から結核菌が検出された各群166例，57例，108例についてQFTの結果を検討した。陽性率は78.3%，75.4%，64.8%，陰性率は7.2%，3.5%，15.7%で，後期高齢者は非高齢者に比し陽性率が低かった（Table 5）。

非高齢者群，前期高齢者群，後期高齢者群間の統計学的解析結果をTable 6に示した。3群間ではPS，他疾患治療中の結核発症，副作用の出現，死亡退院，QFT陽性率，QFT陰性率に有意差が認められた。

Table 1 Clinical characteristics of the patients on admission

	Younger group ≦64 years (N=187)	Early elderly group 65–74 years (N=74)	Late elderly group ≧75 years (N=153)
Sex (Male/Female)	141/46	54/20	89/64
Age (median)	45.6±13.0 (43)	69.8±2.79 (70)	84.4±6.04 (80)
PS 0	56	12	8
1	95	29	34
2	11	15	28
3	11	6	22
4	14	12	61
Albumin＜3.0 g/dl	43 (23.0%)	30 (40.5%)	80 (52.3%)
Without serious underlying disease	112 (59.9%)	16 (21.6%)	32 (20.9%)
Main complications			
DM	25	21	24
HIV	4	0	0
Malignancy	6	11	12
Advanced Dementia	1	3	23
Others	25	27	63

PS: performance status, DM: diabetes mellitus, HIV: human immunodeficiency virus