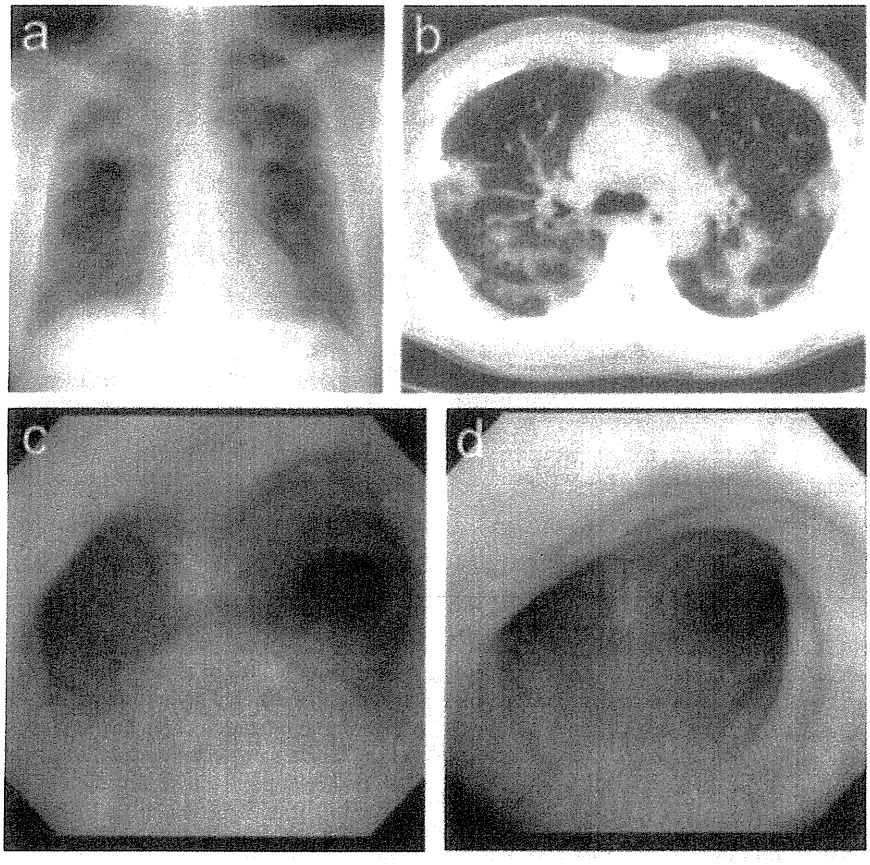

Fig. 3 – Radiological and bronchoscopic findings in Case 2. (a) Chest radiograph at admission showing bilateral consolidations in the upper lung fields. (b) Computed tomography of the chest at admission showing bilateral consolidations in the middle lung fields and periphery. (c) Multiple whitish nodules on the tracheobronchial mucosa, as revealed by fiberoptic bronchoscopy five days after admission. (d) Disappearance of the tracheobronchial nodules 21 days after steroid therapy began.

carina revealed infiltration and degranulation of eosinophils in the subepithelial layer with thickening of the associated basement membranes and squamous metaplasia (Fig. 4a and b). Histopathologic findings of TBLB tissue revealed eosinophil infiltration in the alveolar walls, which were thickened by fibrotic lesions (Fig. 4c and d). Hence, the patient was diagnosed with CEP and started on a steroid treatment regimen. The pulmonary infiltrates and bronchial nodules disappeared 21 days after the initiation of therapy (Fig. 3d).

3.3. *Characteristics*

In order to identify the clinicopathological features of EP patients with multiple nodules in the bronchial mucosa, we classified the patients into 3 groups for analysis: CEP with nodules, CEP without nodules, and Other EP. Although we could not compare the data statistically because of the small number of patients, both patients afflicted by CEP with nodules had never smoked and exhibited coughs, sputum, fevers, high peripheral WBC and eosinophil counts, high bronchoalveolar total cell counts, and eosinophilia (Table 2).

4. Discussion

Although the number of patients was small, to the best of our knowledge, this is the first study describing the frequency of tracheobronchial nodular lesions in EP, and their associated clinical features. Tracheobronchial nodules were seen in 6.9% of CEP patients and in 5.6% of EP patients as a whole. The CEP patients with tracheobronchial nodules both had severe respiratory symptoms and elevated inflammatory markers. Another strength of the present study was that the data were based on an investigation of 36 EP patients who underwent bronchoscopy.

Fox et al. described a CEP patient as having small, pale nodules in the bronchi [11], while Toyoshima et al. reported on a CEP patient with multiple nodular lesions in the trachea and bronchi. In the latter case, peripheral blood eosinophil levels were highly elevated, and a biopsy specimen of the nodule revealed necrotizing bronchial inflammation with pervasive eosinophils. These tracheobronchial lesions resolved after corticosteroid treatment [12]. Similarly, patients with CSS, which is part of the EP spectrum, have been reported to exhibit multiple tracheobronchial lesions [18,19]. Alvarez et al. described such

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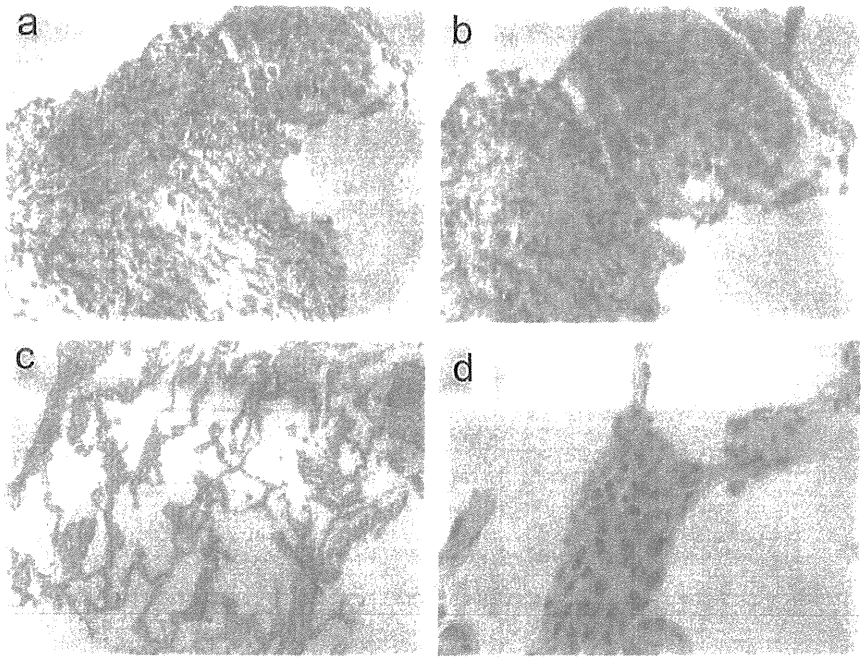

Fig. 4 – Histopathological findings in Case 2. (a–d) Bronchoscopic biopsy samples taken at the time of Fig. 3(c). (a) The biopsy sample taken at the tracheal bifurcation shows squamous metaplasia of the epithelial layer and eosinophil infiltration in the epithelial and subepithelial layers (H&E stain, × 40 objective). (b) A higher magnification of (a). Eosinophils have infiltrated the epithelial and subepithelial layers (H&E stain, × 60 objective). (c) A lung tissue sample taken from the right upper lobe (rt S^3) showing fibrotic thickening of the alveolar walls measuring upto 25 μm, accompanied by infiltration of eosinophils and lymphoid cells. Alveolar structures were kept essentially intact (H&E stain, × 10 objective). (d) A higher magnification of (c). Several eosinophils have infiltrated the alveolar wall, and 2 eosinophils are present in the adjacent alveolar space (H&E stain, × 60 objective).

a CSS patient with tracheobronchial nodules in whom histological observations of eosinophil infiltration and an elevated eosinophil count in BAL fluid were noted [18]. Matsushima et al. likewise reported 2 CSS cases with marked peripheral eosinophilia. Histopathology of the tracheobronchial mucosal lesions revealed necrotizing bronchial inflammation with numerous eosinophils. As with our CEP patients, the bronchial nodules disappeared after steroid treatment [19]. In both of our cases, histopathologic examination of the nodules on bronchial mucosa revealed eosinophil infiltration in the subepithelial regions: after steroid therapy, the nodules and infiltration disappeared (as confirmed by rebiopsy specimens), as did the consolidations observed by chest radiograph and HRCT. Furthermore, in dogs, infiltrations of the airways and/or pulmonary parenchyma by eosinophils have been described as eosinophilic bronchopneumopathy [20]. It should be noted that canine bronchial lesions are closely similar to the human equivalents in the literature and to the present cases, in terms of macroscopic bronchoscopic features, histological findings, and the response to steroids. Taken together, these findings suggest that the observed tracheobronchial nodules are one feature of EP, which disappear in association with decreased allergic inflammation after steroid treatment.

Both of the CEP patients with nodules in this study had high peripheral WBC and eosinophil counts and elevated BAL fluid total and eosinophil cell counts. Both suffered from coughing, sputum, and fever. These cases resembled the CEP patient with tracheobronchial nodules described by Fox et al. That patient also had an elevated WBC count with 30% eosinophils, a cough, and a high-grade fever [11]. Likewise, the patient reported by Toyoshima et al. had an elevated WBC count with 43.7% eosinophils [12]. These findings suggest that tracheobronchial nodules could reflect severe EP. In bronchial asthma, the extent of eosinophilic inflammation of the airways is correlated with disease severity [21]. Therefore, we conclude that the tracheobronchial inflammatory nodules observed in these cases of CEP with nodules were probably associated with a severe manifestation of EP.

Our study had some limitations. First, it was a retrospective study. Second, the positive MPO-ANCA levels observed for Case 2 indicate that the patient may have had CSS. However, his symptoms and laboratory data did not match the diagnostic criteria for CSS. Third, because of the small number of patients with CEP with nodules, we could not compare this group with the other two—CEP without nodules and Other EP—by way of statistical analysis.

5. Conclusions

The presence of tracheobronchial nodules as observed via bronchoscopy should be considered as indicative of severe

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EP. An additional, larger-scale study is necessary to elucidate the precise prevalence of this condition and to confirm the characteristics of such tracheobronchial lesions in the EP patient population.

Conflict of interest

The authors have no conflicts of interest.

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REFERENCES

[1] Liebow AA, Carrington CB. The eosinophilic pneumonias. Medicine (Baltimore) 1969;48:251–85.
[2] Allen JN, Davis WB. Eosinophilic lung diseases. Am J Respir Crit Care Med 1994;150:1423–38.
[3] Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 1989;321:569–74.
[4] Carrington CB, Addington WW, Goff AM, et al. Chronic eosinophilic pneumonia. N Engl J Med 1969;280:787–98.
[5] Cooper Jr. JA, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: Noncytotoxic drugs. Am Rev Respir Dis 1986;133:488–505.
[6] Cordier J-F, Cottin V. Eosinophilic pneumonia. In: Schwarz MI, King Jr TE, Interstitial lung disease, 5th ed.. Shelton, CT: People's Medical Publishing House; 2011. p. 833–93.
[7] Colby TV, Carrington CB. Interstitial lung disease. In: Thurlbeck WM, Churg Am, Pathology of the lung, 2nd ed. New York: Thieme Medical Publishers; 1995. p. 665–72.
[8] Lombard CM. Eosinophilic pneumonia. In: Saldana MJ, Pathology of pulmonary disease. Philadelphia: J.B. Lippincot Company; 1994. p. 745–53.
[9] Jederlinic PJ, Sicilian L, Gaensler EA. Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine (Baltimore) 1988;67:154–62.
[10] Mayo JR, Muller NL, Road J, et al. Chronic eosinophilic pneumonia: CT findings in six cases. Am J Roentgenol, 153; 727–30.
[11] Fox B, Seed WA. Chronic eosinophilic pneumonia. Thorax 1980;35:570–80.
[12] Toyoshima M, Suda T, Chida K. Tracheobronchial involvement in chronic eosinophilic pneumonia. Am J Respir Crit Care Med 2012;186:1057.
[13] Matsuda Y, Tachibana K, Sasaki Y, et al. Two cases of eosinophilic pneumonia with multiple nodules in the bronchial mucosa. Respirology 2008;13:A125.
[14] Mochizuki Y, Kobashi Y, Nakahara Y, et al. Chronic eosinophilic pneumonia–a follow-up study of 12 cases. Nihon Kokyuki Gakkai Zasshi 2002;40:851–5 [in Japanese].
[15] Tillie-Leblond I, Tonnel AB. Allergic bronchopulmonary aspergillosis. Allergy 2005;60:1004–13.
[16] Allen JN. Drug-induced eosinophilic lung disease. Clin Chest Med 2004;25:77–88.
[17] Kurashima K, Mukaida N, Fujimura M, et al. A specific elevation of RANTES in bronchoalveolar lavage fluids of patients with chronic eosinophilic pneumonia. Lab Invest 1997;76:67–75.
[18] Alvarez-Sala R, Prados C, Armada E, et al. Congestive cardiomyopathy and endobronchial granulomas as manifestations of Churg-Strauss syndrome. Postgrad Med J 1995;71:365–6.
[19] Matsushima H, Takayanagi N, Kurashima K, et al. Multiple tracheobronchial mucosal lesions in two cases of Churg-Strauss syndrome. Respirology 2006;11:109–12.
[20] Clercx C, Peeters D. Canine eosinophilic bronchopneumopathy. Vet Clin North Am Small Anim Pract 2007;37:917–35.
[21] Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. N Engl J Med 1990;323:1033–9.

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Original article

Predictors of the clinical effects of pirfenidone on idiopathic pulmonary fibrosis

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with a poor prognosis. Recently, pirfenidone was reported to slow the rate of decline in vital capacity and improve progression-free survival in IPF. The purpose of this study was to clarify the factors that predicted a good response to pirfenidone, as well as its adverse effects.
Methods: Forty-one IPF cases, treated with pirfenidone from January 2009 to January 2011, were enrolled in this investigation. Disease severity was classified into grades I–IV, as defined by the Japanese Respiratory Society (JRS). Short-term responsiveness to pirfenidone was evaluated by the modified criteria of the JRS. Predictors of nausea, anorexia, or both that represented important adverse effects were examined by multivariate Cox proportional

Abbreviations: IPF, Idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; SLB, surgical lung biopsy; VC, vital capacity; NHO-KCCMC, National Hospital Organization Kinki-Chuo Chest Medical Center; UIP, usual interstitial pneumonia; HRCT, high-resolution computed tomography; ATS, American Thoracic Society; ERS, European Respiratory Society; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; KL-6, Krebs von den Lungen-6; (SP)-D, surfactant protein-D; MRC, Medical Research Council; PaO_2, arterial oxygen tension; PPIs, proton pump inhibitors; H2RAs, histamine H2-receptor antagonists

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Anorexia
Acid-secretion inhibitors

hazard analyses. Predictors of short-time responsiveness were examined by multivariate logistic regression analyses.

Results: Diagnosed by a surgical lung biopsy (SLB), the mild cases of grade I/II were predictors of good, short-term responsiveness. Patients taking acid-secretion inhibitors, including proton pump inhibitors and histamine H2-receptor antagonists, showed less anorexia, nausea, or both. Only 1 case was administered drugs to activate gastrointestinal motility.

Conclusions: We concluded that IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of anorexia, nausea, or both from pirfenidone.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a lung disease with a poor prognosis that includes the progressive deterioration of pulmonary function. Its etiology is unknown, and there is no proven effective therapy [1,2]. The pathophysiology of IPF is not fully understood; however, treatments targeting the fibrotic pathway and epithelial injury are supposed to attenuate IPF progression [3].

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) elicits both antifibrotic and anti-inflammatory effects in experimental pulmonary fibrosis models [4]. Open-label studies have revealed that pirfenidone stabilizes IPF disease progression [5,6]. A phase III clinical trial conducted in Japan showed that vital capacity (VC) declined to a lesser degree in pirfenidone-treated IPF patients than that of placebo-treated patients [7]. A significant difference in the progression-free survival was also observed between the 2 groups. On the basis of these findings, in 2008, pirfenidone was approved for IPF treatment in Japan. However, Noble et al. reported controversial results from 2 concurrent phase III trials in the United States [8].

The adverse effects of pirfenidone have been frequently observed. A phase II trial showed that 98.5% of pirfenidone-treated IPF patients had complications including various adverse effects as compared to that of 88.9% of the placebo group [9]. Photosensitivity, nausea, anorexia, and fatigue were observed in 43.8%, 21.9%, 31.5%, and 21.9%, respectively, of the patients; moreover, a significant increase in the frequency of these side effects was observed in the pirfenidone group than that of the placebo group. Photosensitivity can be controlled by prophylactic sunscreen use, which is recommended in the guideline of Shionogi & Co., Ltd. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone.

Thus, if we can predict the responsiveness and adverse effects of pirfenidone treatment in IPF patients, treatment regimens could be better managed. In this study, we examined the predictors of responsiveness and adverse effects of pirfenidone in IPF patients treated in our institute.

2. Materials and methods

2.1. Subjects

From January 1, 2009 to January 1, 2011, 41 patients with IPF were prospectively enrolled and treated with pirfenidone (Shionogi & Co., Ltd., Osaka, Japan) in National Hospital Organization Kinki-Chuo Chest Medical Center (NHO-KCCMC). Informed consent was obtained from all subjects. The institutional review board at NHO-KCCMC approved this study (approval number: Jutaku-20-22; approval date: January 16, 2009). Twenty-three patients were clinically diagnosed with IPF with an usual interstitial pneumonia (UIP) pattern using high-resolution computed tomography (HRCT), while 18 patients were histologically diagnosed as IPF/UIP by surgical lung biopsy (SLB) specimens under the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society guidelines for IPF [10]. HRCT patterns (*e.g.*, UIP pattern or possible UIP pattern) upon pirfenidone initiation were also evaluated in IPF/UIP cases. The patients' demographics are summarized in Table 1.

Table 1 – Patient demographics at the commencement of pirfenidone.

Parameters	Frequency or median (IQR)
Total (*n*)	41 cases
Gender, male (*n*)/female (*n*)	34/7
Age, (years)	70 (65.5–75.5)
Smoking status (*n*), CS/ES/NS	6/24/11
Diagnosis (*n*), Clinical/SLB	23/18
Modified MRC scale (*n*), grade 0/1/2/3/4	2/6/18/12/3
VC, %predicted (%)	66.7 (54.8–77.8)
Severity grade of IPF (*n*), I/II/III/IV	9/5/9/18
Serum KL-6 (U/mL)	858 (1600 – 687)
Serum SP-D (ng/mL)	187 (138–299)
Serum cholinesterase (U/L)	270 (216–327)
Long term oxygen therapy (*n*), Yes/No	22/19
Treatment before pirfenidone	
Corticosteroid alone (*n*)	3
Corticosteroid and azathioprine (*n*)	4
Corticosteroid and cyclosporine (*n*)	1
Inhalation of N-acetyl-cysteine (*n*)	1

Abbreviations: IQR, interquartile range; CS, current smokers; ES, ex-smokers; NS, non-smokers; SLB, surgical lung biopsy; MRC scale, Medical Research Council score for shortness of breath upon exertion; VC, vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein-D.

2.2. Clinical parameter measurement

Pulmonary function tests, including VC, total lung capacity (TLC), and diffusing capacity of carbon monoxide (DLco), were performed using CHESTAC-8800 (Chest M.I., Inc., Tokyo, Japan). A 6-min walk test was performed in accordance with ATS guidelines [11]. Serum Krebs von den Lungen-6 (KL-6) and surfactant protein-D (SP)-D were measured by the enzyme-linked immunosorbent assay using commercially available kits [12]. Dyspnea was assessed by the modified Medical Research Council (MRC) scale from the ATS/ERS [13].

2.3. IPF severity grade

The IPF severity grade was classified per the JRS criteria [7] using the arterial oxygen tension (PaO_2) at rest and minimum SpO_2 during a 6-min walk test performed before pirfenidone initiation. Patients with a $PaO_2 \geq 80$ Torr were classified as grade I; ≥ 70 Torr and <80 Torr as grade II; ≥ 60 Torr and <70 Torr as grade III; and <60 Torr as grade IV. For patients with $\geq$ grade II, if the SpO_2 during a 6-min walk test was $<90\%$, then the severity grade was increased by one grade.

2.4. Pirfenidone administration

Pirfenidone daily dosing was increased in a stepwise manner from 600 to 1800 mg every 2 weeks [7]. The median maximum dose was 1800 mg (range, 600–1800 mg), and the median final dose in the treatment period was 1200 mg (range, 600–1800 mg). The dose was decreased in accordance with the occurrence of adverse events. The median observation period for each IPF patient administered pirfenidone was 400 days (range, 12–885 days).

2.5. Pirfenidone response

A comprehensive evaluation of the patients was performed regarding short-term responsiveness at 3–6 months after pirfenidone initiation to classify the patients as experiencing either an improvement (good response) or a deterioration of at least 2 of the 3 parameters (clinical symptoms, radiological findings, and physiological findings) according to modified criteria [14] of JRS, as well as King et al. [15] on the basis of a prior ATS/ERS consensus statement on IPF that was published in 2000 [16]. Stable state was defined as neither improvement nor deterioration. Evaluation of each parameter is defined in the online supplement (Table S1 in the online supplementary data).

The effects of pirfenidone in 10 IPF cases could not be evaluated because of death ($n=1$; pirfenidone treatment, 12 days), transfer to other hospitals ($n=1$; pirfenidone treatment, 88 days), or pirfenidone withdrawal because of adverse effects ($n=8$; pirfenidone treatment range, 10–65 days) within 3 months of initiation. Thus, short-term responsiveness was evaluated in 31 cases. One patient who died within 3–6 months of pirfenidone initiation was evaluated as *deteriorated*.

2.6. Evaluation and treatment of adverse effects, including anorexia, nausea, or both

Adverse effects in all cases were evaluated using the Common Terminology Criteria for Adverse Events (v. 4). Acute exacerbation of IPF was defined according to the criteria in Japan [7,14]. Of all adverse effects, we evaluated nausea or anorexia that would be classified as $\geq$ grade 2. In grade 2, oral ingestion decreased without significant weight loss; in grade 3, hospitalization was necessary because of significant weight loss secondary to inadequate oral ingestion. Drugs to protect the gastric mucosa and activate gastric motility, including proton pump inhibitors (PPIs) and histamine H2-receptor antagonists (H2RAs), were administered before IPF treatment because of comorbidities that included chronic gastritis, gastric/duodenal ulcers, and gastroesophageal reflux disease. The PPIs, including omeprazole, lansoprazole, and rabeprazole, were administered to 2, 5, and 9 cases, respectively. Cimetidine (H2RA) was administered to 3 cases. Each patient was additionally prescribed several types of drugs for gastrointestinal symptoms if nausea, anorexia, or both occurred.

2.7. Statistical analyses

Patient demographics data are presented as frequency (%) or median with a range. Correlation between pirfenidone response and IPF severity grade was examined by Fisher's exact test and Spearman rank correlation. Univariate and multivariate logistic regression analyses were performed to clarify the predictors of pirfenidone responsiveness. Each numerical parameter was divided into 2 groups by the median. For grades ≥ 2, the Kaplan–Meier method was used to assess the occurrence of nausea, anorexia, or both as adverse effects according to *time without nausea/anorexia* for IPF patients taking pirfenidone. Clinical parameters determining the occurrence of anorexia, nausea, or both were examined by univariate and multivariate Cox proportional hazard regression analyses. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (v.19) (Chicago, IL, USA).

3. Results

3.1. Short-term pirfenidone response and IPF severity stage

Physiological and radiological improvements were observed in 4 cases and 2 cases, respectively. Symptoms improved in 11 cases (cough, 8 cases; shortness of breath, 6 cases). A comprehensive assessment revealed that 6 cases improved 3–6 months after pirfenidone initiation. The patients' pirfenidone response was found to be significantly associated with the IPF severity grade using the Fisher's exact test ($P=0.025$) and Spearman rank correlation ($\rho=0.5039$; $P=0.0039$) (Table 2).

3.2. Predictors of short-term pirfenidone response

Using the 2 significant parameters as determined by the univariate analysis (Table S2 in the online supplementary data), the multivariate analyses (Table 3) showed that diagnosis with

Table 2 – Short-term response to pirfenidone.

	Severity grade of IPF			
	I	II	III	IV
n	8	3	8	12
VC, %predicted (IQR) (%)	76.6 (69.7–83.2)	87.6 (86.0–88.9)	64.8 (57.7–71.7)	58.9 (47.7–64.5)
Response to pirfenidone				
Improvement (*n*)	3	2	1	0
Stable (*n*)	5	1	3	7
Deterioration (*n*)	0	0	4	5

Abbreviations: IPF, idiopathic pulmonary fibrosis; VC, vital capacity; IQR, interquartile range. Significant correlation between response to pirfenidone and severity grade of IPF was observed by Fisher's exact test ($p=0.025$). Definition of severity grade and response of pirfenidone was described in Section 2 and Table S1 in the online supplementary data.

Table 3 – Predictors of short-term good response to pirfenidone[a]

Factors	Odds ratio	95% CI	*p*-value
Severity grade (I/II)	32.988	1.813–600.319	0.018
Diagnosis (SLB)	23.651	1.265–442.125	0.034

Abbreviations: CI, confidence interval; SLB, surgical lung biopsy; IPF, idiopathic pulmonary fibrosis.

[a] Univariate logistic regression analysis was performed using age (≤70 years), smoking status (non-smoker), diagnosis by SLB, severity grade (I/II), Modified Medical Research Council scale for shortness of breath upon exertion (0–1), cholinesterase (>270 U/L), Krebs von den Lungen-6 (>858 U/mL), surfactant protein-D (>187 ng/mL) and usage of proton pump inhibitor (Table S2 in the online supplementary data). Multivariate logistic regression analysis was performed using significant parameters by univariate analysis (*e.g.* diagnosis with SLB and severity grade of IPF) (Table S2).

SLB specimens was a significant predictor, in addition to an IPF severity grade of I/II. Similar results were found in the evaluable short-term response cases after the addition of 1 deceased case that had died 12 days after pirfenidone initiation. No difference was observed between clinical IPF and IPF/UIP at pirfenidone initiation, except for age, gender, and HRCT patterns (Table S3 in the online supplementary data).

3.3. *VC change before and after pirfenidone initiation*

A change (L/year) in VC could be compared between 3 and 12 months before and 3 and 6 months after pirfenidone initiation by the Wilcoxon signed-rank test in 21 cases. In patients with severity grade I/II, the change in VC significantly decreased after pirfenidone initiation ($n=10$; $P=0.0039$) (Fig. 1A). However, the VC change did not significantly decline in IPF patients with severity grade III/IV ($n=11$; $P=0.1748$) (Fig. 1B). Patients with severity grade I/II experienced a VC change before pirfenidone administration that was significantly smaller than that of patients with severity grade III/IV using the Wilcoxon rank-sum test ($P=0.0290$).

3.4. *Pirfenidone adverse effects*

Adverse effects were observed in 31 of the 41 IPF patients (75.6%) following pirfenidone initiation. Anorexia, nausea, or both were

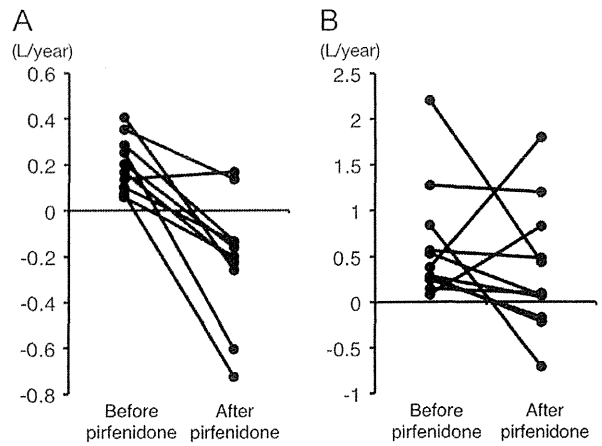

Fig. 1 – A change in vital capacity (VC; L/year) was compared with the Wilcoxon signed-rank test between 3 and 12 months before and 3 and 6 months after pirfenidone initiation with (A) severity grade I/II ($n=10$) and (B) severity grade III/IV ($n=11$). In severity grade I/II patients, the change in VC significantly decreased after pirfenidone initiation ($p=0.0039$) (A). However, the change in VC did not significantly decline in severity grade III/IV patients ($p=0.1748$) (B). The change in VC before pirfenidone administration in severity grade I/II patients was significantly smaller than that of severity grade III/IV patients with Wilcoxon rank-sum test ($p=0.0290$).

observed in 24 of the 41 (58.5%) IPF patients. Other adverse effects were photosensitivity (5 cases, 12.2%), allergic skin reaction (2 cases, 4.9%), sleepiness (2 cases, 4.9%), photophobia (1 case, 2.4%), vertigo (1 case, 2.4%), diarrhea (1 case, 2.4%), and acute exacerbation (4 cases, 9.8%). Pirfenidone was ceased in 15 cases (34.1%) because of anorexia, nausea, or both (6 cases, 14.6%); disease progression including acute exacerbation (7 cases, 17.1%); and transfer to other hospitals (2 cases, 4.9%). Six cases (14.6%) died from disease progression.

3.5. *Pirfenidone induced anorexia, nausea, or both*

Nineteen IPF cases (acid-secretion inhibitor group) were taking PPIs or H2RAs before pirfenidone initiation as treatment for

Table 4 – Prophylactic effects of acid-secretion inhibitors on anorexia and/or nausea due to pirfenidone.

Drugs at the introduction of pirfenidone	No. of cases	Anorexia and/or nausea	Dose reduction of pirfenidone		
			None	Reduction	Withdrawal
Acid-secretion inhibitors[a] (*n*)	19	8	3	4	1
No acid-secretion inhibitors[b] (*n*)	22	16	7[c]	4	5

Frequency of anorexia and/or nausea was significantly less in the acid-secretion inhibitors group than that in the no acid-secretion inhibitors group as determined by the chi-square test ($p<0.05$).

[a] Proton pump inhibitors (PPIs) or histamine H2-receptor antagonists (H2RA) were administered. The PPIs, omeprazole, lansoprazole, and rabeprazole, were administered to two, five, and nine cases, respectively. The H2RA, cimetidine, was administered in three cases.

[b] Acid-secretion inhibitors were not administered, but drugs for gastritis, drugs to protect gastric mucosa or to activate motility of the gastrointestinal tract were administered. Gastrointestinal drugs in detail were shown in Table S4 in the online supplementary data.

[c] Anorexia and/or nausea improved after the additional use of PPIs after the onset of the adverse effects.

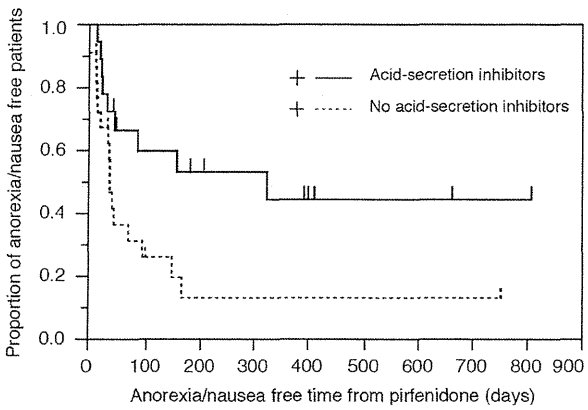

Fig. 2 – Kaplan–Meier plots of anorexia/nausea-free time in IPF patients administered pirfenidone and acid-secretion inhibitors (solid line) or pirfenidone alone (dotted line). The median anorexia/nausea-free time from pirfenidone initiation to the onset of anorexia/nausea in patients with ≥ grade 2 was significantly shorter in cases with no acid-secretion inhibitors (34 days) than in cases with acid-secretion inhibitors (324 days), as determined by log-rank test ($p=0.0211$). Cases that continued pirfenidone treatment and then stopped because of other adverse events, other than anorexia, nausea, or both, were treated as censored cases.

other comorbidities (Table 4). The other 22 cases (no acid-secretion inhibitor group) were not administered acid-secretion inhibitors but administered drugs to protect the gastric mucosa. No significant difference in frequency of coadministered gastrointestinal drugs was observed between the 2 groups (Table S4 in the online supplementary data). One case was administered drugs to activate gastrointestinal motility. There was no difference in pirfenidone dose between the 2 groups.

In the no acid-secretion inhibitor group, 16 cases (72.7%) complained of anorexia, nausea, or both, and 5 cases (22.7%) ceased taking pirfenidone; however, 7 cases continued to take pirfenidone because of additional PPI usage. In the acid-secretion inhibitor group, anorexia, nausea, or both occurred in only 8 cases (42.1%), and almost all cases remained on pirfenidone but with a dose reduction (Table 4). The χ^2 tests revealed that anorexia, nausea, or both occurred at a significantly lower frequency in the acid-secretion inhibitor group ($P<0.05$). The anorexia-free time (median, days) in the IPF patients administered pirfenidone in the acid-secretion inhibitor group was 324 days (Kaplan–Meier method), and this was significantly longer than that of the no acid-secretion inhibitor group (34 days) (Fig. 2).

Table 5 – Predictors of nausea and/or anorexia caused by pirfenidone[#]

Factors	Risk ratio	95% CI	*p*-value
Acid-secretion inhibitors (No[a])	2.346	1.053–5.591	0.037
Age (>70 years)	1.910	0.868–4.410	0.1083

Abbreviations: PPI, proton pump inhibitor; CI, confidence interval.

[#] Multivariate Cox proportional Hazard analysis was performed using two parameters with *p*-value less than 0.10 by univariate Cox proportional Hazard analysis using age (>70 years), smoking status (non-smoker), diagnosis (clinical), severity grade (IV), Modified Medical Research Council scale for shortness of breath upon exertion (0–2), serum cholinesterase (>270 U/L), no administration of acid-secretion inhibitors and administration of prednisolone described in Table S5 in the online supplementary data.

[a] PPIs and histamine H2-receptor antagonists was not administered at the commencement of pirfenidone.

3.6. *Predictors of anorexia, nausea, or both with pirfenidone administration*

A univariate analysis (Table S5 in the online supplementary data) using the Cox proportional hazard regression analyses revealed that the lack of acid-secretion inhibitors was the only significant factor. Prednisolone administration did not affect the onset of nausea, anorexia, or both. The multivariate analyses using factors with a P-value of <0.10 (Table 5) showed that the lack of acid-secretion inhibitors was a significant predictor of anorexia, nausea, or both.

4. Discussion

Our investigation demonstrated that the IPF severity grade (I/II) was a significant predictor of a short-term, good response to pirfenidone. Azuma et al. [17] performed an exploratory analysis in a phase III pirfenidone trial and reported that pirfenidone was effective in IPF patients with a %VC ≥ 70% or PaO_2 ≥ 70 Torr and

a SpO_2 <90% during a 6-min walk test at baseline, as compared to that of the placebo group. Their criteria for good responders corresponded to IPF cases with mild-to-moderate lung function impairment, although it was not necessarily similar to stage I/II per the JRS criteria. IPF cases with severity grade I/II also had a significant decrease in VC change after pirfenidone initiation. Thus, pirfenidone might have some effects in the unimproved grade I/II cases.

Another important predictor of a good response to pirfenidone was diagnosis by SLB specimens. Five of the 6 IPF cases with a good, short-term response to pirfenidone were diagnosed by an SLB. Similar results were reported in a bosentan clinical trial for IPF [18]. These results might be explained by the hypothesis that the beneficial effect was greater in IPF cases with a possible UIP pattern on HRCT. It is true that all the IPF/UIP cases in our study demonstrated a possible UIP pattern at diagnosis; however, the HRCT pattern in 8 of the 13 IPF/UIP cases was a definite UIP pattern upon pirfenidone initiation, and 3 of the 5 IPF/UIP cases that had a good response to pirfenidone exhibited a definite UIP pattern. Thus, other factors supposedly have an effect on a good response, although the HRCT pattern might be partially associated with a good response. A detailed reevaluation of the pathological and radiological findings may be warranted to determine the features associated with a good response to pirfenidone.

We performed a multidisciplinary evaluation of a pirfenidone response using radiological and symptomatic parameters, in addition to physiological parameters. Iwashita et al. reported that the radiological findings have improved in only 3 of the 38 cases 1 year after pirfenidone initiation [19], which is consistent to our result. However, our investigation showed that radiologic improvement could be observed in shorter treatment periods, 3–6 months after pirfenidone initiation. The degree of cough had not been evaluated in previous reports. We observed a cough improvement in some cases, although it remains unclear if this was because of a direct effect of pirfenidone. Acute exacerbation of IPF was not inhibited by pirfenidone in the phase III trials [7]. However, the incidence of acute exacerbation in our population (9.8%) was high, as compared with that of the previous clinical trials [7,9]. This may have occurred because severe cases were included in this study.

Taniguchi et al. reported that the short-term effects could predict the long-term effects of pirfenidone, using data from a Japanese phase III clinical trial [20]. They evaluated pirfenidone-treated IPF patients for 3 months and categorized them into 2 groups: a "worsening" group with a relative VC decline of $\geq 5\%$ and a "no worsening" group with no such decline. For 71.7% of the pirfenidone-treated cases in the "no worsening" group, no deterioration occurred 1 year posttreatment, while 87.1% of the pirfenidone-treated cases in the "worsening" group deteriorated 1 year posttreatment. In our examination, 5 of the 6 short-term improvement cases remained on pirfenidone for >1 year, and 4 of the 5 cases were evaluated as stable (data not shown). Although our investigation of the long-term effects was not sufficient, evaluation of the short-term effects may be useful for predicting long-term responsiveness.

Pirfenidone is a promising drug for IPF; however, adverse effects (photosensitivity and anorexia and/or nausea) frequently occurred in several clinical trials [5–7,9]. Gastrointestinal adverse effects are the most important dose-limiting and withdrawal-determining factors of pirfenidone. Our investigation showed the possible preventive effects of PPIs and H2RA against nausea, anorexia, or both.

The pathophysiology of anorexia and nausea with pirfenidone administration has not been fully elucidated; however, it might be associated with the suppression of gastrointestinal motility [21]. Although gastroscopy was not performed on any of our cases, we do not believe anorexia occurred from gastroduodenal ulcers, as it spontaneously resolved after pirfenidone discontinuation. PPIs and H2RAs do not directly activate gastric motility; however, they are known to improve postprandial fullness and early satiation observed in functional dyspepsia without organic disease [22] through attenuating duodenal hypersensitivity to acids [23]. It is reported that PPI monotherapy improves dysmotility-like symptoms significantly better than that of H2RAs plus mosapride in functional dyspepsia [24].

The effect of PPIs on the pharmacokinetics of pirfenidone is an important problem. Although neutralizing acid does not affect pirfenidone absorption or its plasma concentration [25], drug interactions between PPIs and pirfenidone should be considered. *In vitro* metabolism studies revealed that approximately 48% of pirfenidone is metabolized via cytochrome P450 (CYP) 1A2, while <13% is done so by each of CYP2C9, 2C19, 2D6, and 2E1 [26]. PPIs inhibit some CYP reactions; however, all the CYPs associated with pirfenidone metabolism are not simultaneously inhibited [27], and we postulate that the inhibitory effects of pirfenidone may be clinically limited.

In vitro evaluations using hepatoma cell-lines showed that CYP1A2, the most important metabolizer of pirfenidone, was induced by omeprazole and lansoprazole, but not by rabeprazole [28]. Thus, omeprazole and lansoprazole may accelerate pirfenidone metabolism and theoretically decrease its serum concentration and clinical effects; however, *in vitro* studies are not always consistent with *in vivo* studies. *In vivo* interactions of theophylline and caffeine, which are metabolized by CYP1A2, with omeprazole could be clinically negligible in accordance to pharmacokinetic studies [29]. Although the coadministration of pirfenidone and PPIs might not affect the *in vivo* clinical effects, rabeprazole is better than omeprazole and lansoprazole from the standpoint of CYP1A2 induction. Rabeprazole was administered to 2 of the 6 improved cases in our examination (data not shown). Esomeprazole may be another important PPI, as it does not interact with drugs metabolized by CYP1A2 [30].

As for H2RAs, cimetidine is known to interfere with the metabolism of many drugs by inhibiting CYP3A4, CYP1A2, and CYP2D6 [31]. Thus, cimetidine and pirfenidone coadministration might lead to elevated serum pirfenidone levels and deteriorating gastrointestinal symptoms in some cases. Interactions of ranitidine and famotidine with CYP isoenzymes are weak and negligible [32,33].

Our study had several limitations. First, this was not a randomized trial, and PPIs were used for comorbidities. Second, the number of patients was small. Future randomized, controlled trials are necessary to assess the effects of PPIs on nausea, anorexia, or both caused by pirfenidone.

5. Conclusion

IPF patients with a mild disease, diagnosis by SLB, or both showed indications of a good response to pirfenidone. In addition, acid-secretion inhibitors may reduce the frequency of nausea, anorexia, or both from pirfenidone.

Conflict of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary materials

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.resinv.2013.09.002.

REFERENCES

[1] Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157:199–203.
[2] Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994;149:450–4.
[3] Günther A, Korfei M, Mahavadi P, et al. Unravelling the progressive pathophysiology of idiopathic pulmonary fibrosis. Eur Respir Rev 2012;21:152–60.
[4] Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on transforming growth factor-b gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J Pharmacol Exp Ther 1999;291:367–73.
[5] Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label Phase II study. Am J Respir Crit Care Med 1999;159:1061–9.
[6] Nagai S, Hamada K, Shigematsu M, et al. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med 2002;41:1118–23.
[7] Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010;35:821–9.
[8] Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. Lancet 2011;377:1760–9.
[9] Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005;171:1040–7.
[10] Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183:788–824.
[11] ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
[12] Inoue Y, Trapnell BC, Tazawa R, et al. Characteristics of a large cohort of patients with autoimmune pulmonary alveolar proteinosis in Japan. Am J Respir Crit Care Med 2008;177:752–62.
[13] Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J 2004;23:932–46.
[14] The Japanese Respiratory Society. Idiopathic interstitial pneumonia: diagnosis and treatment, 2nd ed.. Tokyo: Nankodo; 2011.
[15] King Jr. TE. Idiopathic pulmonary fibrosis. In: Schwarz MI, King Jr TE, Interstitial lung disease. America: People's Medical Publishing House-USA; 2011. p. 895–944.
[16] American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 2000;161:646–64.
[17] Azuma A, Taguchi Y, Ogura T, et al. Exploratory analysis of a phase III trial of pirfenidone identifies a subpopulation of patients with idiopathic pulmonary fibrosis as benefit from treatment. Respir Res 2011;12:143.
[18] King Jr TE, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008;177:75–81.
[19] Iwasawa T, Ogura T, Sakai F, et al. CT analysis of the effect of pirfenidone in patients with idiopathic pulmonary fibrosis. Eur J Radiol 2012 ([Epub ahead of print]).
[20] Taniguchi H, Kondoh Y, Ebina M, et al. The clinical significance of 5% change in vital capacity in patients with idiopathic pulmonary fibrosis: extended analysis of the pirfenidone trial. Respir Res 2011;12:93.
[21] Itoh T, Koyabu K, Morimoto A, et al. Ameliorative effects of mosapride or Rikkunshi-to on the suppression of gastrointestinal motility by pirfenidone. Jpn Pharmacol Ther 2012;40:405–11.
[22] Brun R, Kuo B. Functional dyspepsia. Ther Adv Gastroenterol 2010;3:145–64.
[23] Ishii M, Kusunoki H, Manabe N, et al. Duodenal hypersensitivity to acid in patients with functional dyspepsia-pathogenesis and evaluation. J Smooth Muscle Res 2010;46:1–8.
[24] Sakaguchi M, Takao M, Ohyama Y, et al. Comparison of PPIs and H2-receptor antagonists plus prokinetics for dysmotility-like dyspepsia. World J Gastroenterol 2012;18:1517–24.
[25] Rubino CM, Bhavnani SM, Ambrose PG, et al. Effect of food and antacids on the pharmacokinetics of pirfenidone in older healthy adults. Pulm Pharmacol Ther 2009;22:279–85.
[26] Esbriet: EPAR-Product Information. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002154/WC500103049.pdf. 07/02/2012).
[27] Zvyaga T, Chang SY, Chen C, et al. Evaluation of six proton pomp inhibitors as inhibitors of various human cytochromes P450: focus on cytochrome 2C19. Drug Metab Dispos 2012;40:1698–711.

[28] Krusekopf S, Roots I, Hildebrandt AG, et al. Time-dependent transcriptional induction of CYP1A1, CYP1A2 and CYP1B1 mRNAs by H+/K+-ATPase inhibitors and other xenobiotics. Xenobiotica 2003;33:107–18.
[29] Dilger K, Zheng Z, Klotz U. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. Br J Clin Pharmacol 1999;48:438–44.
[30] Andersson T, Hassan-Alin M, Hasselgren G, et al. Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001;40:523–37.
[31] Martinez C, Albet C, Agundez JA. Comparative in vitro and in vivo inhibition of cytochrome P450 CYP1A2, CYP2D6, and CYP3A by H_2-receptor antagonists. Clin Pharmacol Ther 1999;65:369–76.
[32] Humphries TJ, Merritt GJ. Review article: drugs interactions with agents used to treat acid-related disease. Aliment Pharmacol Ther 1999;13(Suppl 3):18–26.
[33] Humphries TJ. Famotidine: a notable lack of drug interactions. Scand J Gastroenterol Suppl 1987;134:55–60.

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CASE REPORT Open Access

Development of microscopic polyangiitis-related pulmonary fibrosis in a patient with autoimmune pulmonary alveolar proteinosis

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Abstract

Background: Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare lung disease caused by the autoantibody against granulocyte-macrophage colony stimulating factor (GM-CSF). The clinical course of aPAP is variable; in severe cases, patients develop lethal respiratory failure due to pulmonary fibrosis. However, the pathogenesis of pulmonary fibrosis in aPAP has never been delineated.

Case presentation: Here, we describe a rare case of aPAP that was subsequently complicated by microscopic polyangiitis-related pulmonary fibrosis. The patient was a 75-year-old Japanese man diagnosed with aPAP based on the crazy-paving appearance on high-resolution computed tomography (HRCT), "milky" appearance of broncho-alveolar lavage fluid (BALF), and elevated serum levels of the anti-GM-CSF antibody. The patient was followed-up without aPAP-specific treatment for 3 years. During this period, both hematuria and proteinuria appeared; in addition, serum myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA) turned positive and increased markedly. The second BAL performed one year after the diagnosis, showed that the "milky" appearance had resolved. The HRCT showed that fibrotic changes had developed and that the crazy-paving appearance had disappeared. These data suggest an association between pulmonary fibrosis that developed during the natural course of aPAP and ANCA-related systemic vasculitis.

Conclusion: This is the first case report that suggests the existence of a pathogenetic relationship between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis. The link between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis requires further investigation.

Keywords: Pulmonary alveolar proteinosis, Pulmonary fibrosis, Myeloperoxidase antineutrophil cytoplasmic antibody

Background

Autoimmune pulmonary alveolar proteinosis (aPAP), which causes 90% of all PAP cases, is an autoimmune disease caused by the presence of an autoantibody against granulocyte-macrophage colony stimulating factor (GM-CSF) [1]. The suppression of GM-CSF signaling by anti-GM-CSF autoantibody disrupts the surfactant catabolism, resulting in the accumulation of surfactant lipids and proteins in pulmonary alveolar macrophages and alveoli. The clinical course of aPAP is variable. In the contemporaneous cohort of 223 Japanese aPAP patients, 3 patients (1.4%) were complicated by severe respiratory failure due to pulmonary fibrosis [2]. And so far, there have been, at least, 5 case reports, which highly suggested the pathogenetic relationship between aPAP and pulmonary fibrosis [3-7].

The pathogenesis of pulmonary fibrosis in aPAP is unknown. It has been hypothesized that the retention of lipoproteinaceous material in the alveoli, silica exposure, and/or superimposed pulmonary infections induces damage to cells lining the alveoli and causes pulmonary fibrosis in aPAP patients [5]. In rats, the

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overexpression of GM-CSF in the lung by adenovirus-vector leads to pulmonary fibrosis, suggesting an inconclusive relationship between GM-CSF therapy and pulmonary fibrosis in patients with aPAP [8].

Anti-neutrophil cytoplasmic antibody (ANCA) is a sensitive and specific marker for ANCA-associated systemic vasculitis, as observed in granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), "idiopathic" necrotizing crescentic glomerulonephritis and allergic granulomatous angiitis [9]. In vitro and in vivo studies provide compelling evidence that ANCA play a critical role in the pathogenesis of ANCA-associated systemic vasculitis [10]. Pulmonary fibrosis due to alveolar capillaritis is a common complication in ANCA-associated systemic vasculitis. However, ANCA-related pulmonary fibrosis has never been reported in association with aPAP.

Case presentation

A 75-year-old Japanese man, who self-identified as a chronic smoker (30 pack-years), was referred to our hospital because of a cough, which had been continued for 2 months, and an abnormal chest X-ray. He had no significant past medical history. He was an owner of a liquor shop and had no prior exposure to harmful dust. The physical examination revealed fine crackles bilaterally over the lower lung. The laboratory findings showed elevated levels of lactate dehydrogenase (376 U/L; normal range, 120-242), Krebs von den Lungen-6 (17330 U/mL; normal range, 0-500), surfactant protein-D (293.0 ng/mL; normal range, 0–110), carcinoembryonic antigen (12 ng/mL; normal range, 0–5.0), and CYFRA21.1 (cytokeratin-19 fragments) (26.5 ng/mL; normal range, 0–20.0) in the serum. Serum antinuclear antibody titer was 1:40 (normal range, <1:40), and myeloperoxidase (MPO)-ANCA testing was negative. The chest X-ray showed diffuse bilateral ground-glass opacities, and high-resolution computed tomography (HRCT) showed a crazy-paving appearance (Figure 1A). Bronchoscopy was performed; the broncho-alveolar lavage fluid (BALF) from the left lingura (B^5) showed a

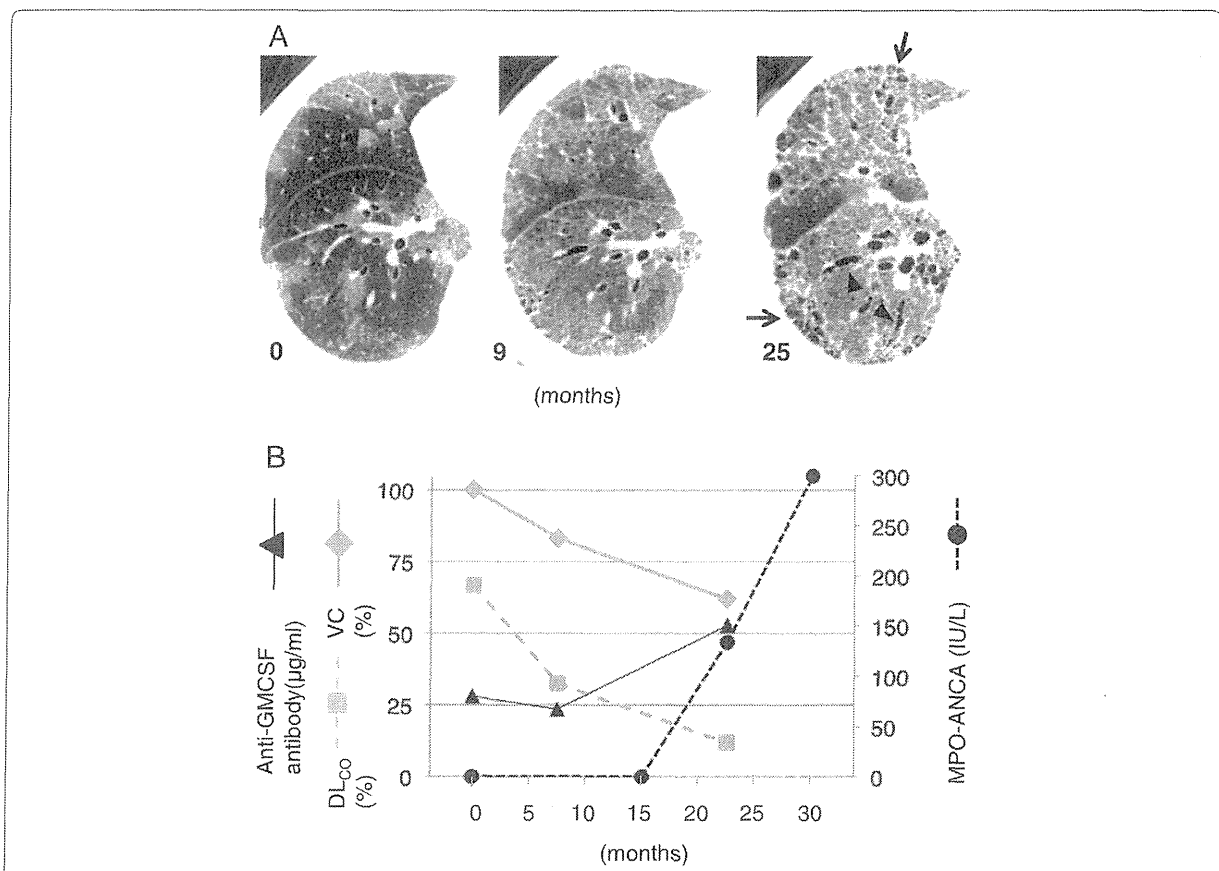

Figure 1 During the clinical course of aPAP in this patient, HRCT images showed increased evidence of pulmonary fibrosis: reticular opacity (arrows) and traction bronchiectasis (arrowheads). (A) Serum MPO-ANCA testing became positive and then increased significantly (circle), while the results of pulmonary function tests, including vital capacity (VC, diamond) and CO diffusing capacity (DLCO, square), deteriorated. Serum anti-GM-CSF antibody concentrations kept high and increased **(B)**.

typical "milky" appearance. The total cell count in BALF was 320/μL. Differential cell count revealed 50% alveolar macrophages, 36% lymphocytes, 12% neutrophils, 2% eosinophils. Pathological examination of a transbronchial lung biopsy sample revealed periodic-acid-Schiff stain-positive material along the alveolar wall. After the serum anti-GM-CSF autoantibody concentration (28 μg/mL; normal range, <0.5) was confirmed and the comorbidity of hematological diseases, such as chronic myelocytic leukemia, myelodysplastic syndrome, or monoclonal gammopathy of undetermined significance, were excluded, the patient was diagnosed with aPAP.

Because the patient refused any specific treatment for aPAP, including whole-lung lavage and GM-CSF inhalation therapy, he was followed in the outpatient department. Nine months later, his cough had worsened and he began to experience dyspnea upon exertion, which was classified using the modified Medical Research Council Dyspnea Scale (mMRC) as grade 2. The chest HRCT obtained at this visit showed that the crazy-paving pattern had been replaced by fibrotic changes, i.e., subpleural honeycombing and traction bronchiectasis (Figure 1A). In contrast to the results obtained at the time of diagnosis, the BALF was transparent, without a "milky" appearance. Serum anti-GM-CSF autoantibody concentration was 23.5 μg/mL. Surprisingly, serum MPO-ANCA testing was positive (134 IU/L) and subsequently continued to rise (Figure 1B). In accordance with the fibrotic changes seen on HRCT images, the patient's respiratory failure had worsened since diagnosis (Figure 1B). The patient also showed signs of hematuria and proteinuria. Although neither kidney nor lung biopsies were performed because of the patient's general condition, the findings presented above met the most recent criteria for MPA [11]. Because the patient refused steroid and immunosuppressant treatment, he has been followed-up for MPA without any specific therapy.

Many studies have shown that ANCA production is key to the pathogenesis of MPA. ANCA is known to activate neutrophils and allow their accumulation at the endothelial portion of a vasculitic lesion [12]. ANCA is also an excellent diagnostic marker of MPA with specificity of 96.3-99.1% [13]. Based on these findings, the European League against Rheumatism and the American College of Rheumatology established new criteria that emphasized serum ANCA in the diagnosis of MPA [14]. A new criterion of MPA, proposed by Watts, lays more emphasis on the role of ANCA in MPA diagnosis, wherein histopathological signs of vasculitis are not essential for the diagnosis [11]. Our case met these criteria due to the patient's high level of MPO-ANCA and the associated urinary findings.

There are several reports of pulmonary fibrosis that developed in patients with aPAP. In these cases, as in ours, the features of PAP disappeared as pulmonary fibrosis progressed [5,7]. As Luisetti et al. mentioned, it is not possible for us to exclude that some subjects diagnosed with diffuse fibrotic lung disease actually represented the end-stage evolution of a previous pulmonary alveolar proteinosis process [7]. If a patient's BALF or HRCT does not show a typical PAP appearance at the time of admission, serum GM-CSF autoantibody is not usually measured. Thus, the link between PAP and pulmonary fibrosis must be explored. In this report, we suggest the role of ANCA-associated systemic vasculitis in the pathogenesis of aPAP-related pulmonary fibrosis. We sought to verify the existence of ANCA-associated systemic vasculitis in patients with aPAP-related pulmonary fibrosis, because in these cases, steroids or immunosuppressants (including rituximab) that are not usually used for the treatment of aPAP may be effective for the treatment of pulmonary fibrosis [15]. There is one reported case of secondary PAP with high levels of MPO-ANCA [16]. Further research will be necessary to elucidate the link between aPAP and ANCA-associated systemic vasculitis. Serum ANCA levels should be examined in cases of aPAP complicated by pulmonary fibrosis.

It is generally thought that autoimmune diseases are induced by dysfunctional immunotolerance to self-antigens due to genetic as well as environmental factors [17]. Clinical evidence shows that the coexistence of autoimmune diseases within an individual (i.e., polyautoimmunity) is not uncommon, suggesting that these autoimmune diseases have a common genetic or environmental root [18]. It is also reported that aPAP sometimes accompanies other systemic or organ-specific autoimmune diseases. Seymour et al. reviewed 410 cases of PAP and reported seven cases (1.7%) with coexisting autoimmune disorders or positive autoimmune serology (rheumatoid arthritis, two cases; anti-smooth muscle antibody positive, two cases; multiple sclerosis, one case; IgA nephropathy, one case; and celiac disease, one case) [19]. Inoue et al. reported three cases among 212 patients with aPAP that were complicated by other autoimmune diseases including polymyalgia rheumatica, GPA, and autoimmune hemolytic anemia [2]. Whether the coexistence of aPAP and ANCA-associated systemic vasculitis in our case was anecdotal or due to shared underlying mechanisms remains to be elucidated. However, it is known that air pollution and/or infections sometimes overwhelm immunotolerance to MPO, even in healthy individuals [20]. Owing to their genetic tendency toward autoimmune disease and the altered immunologic milieu in their lungs, aPAP patients might be prone to developing an autoimmune reaction to MPO, triggered by an unknown environmental factor.

Conclusion

Previous research has not succeeded in explaining why pulmonary fibrosis occurs in patients with aPAP, or how we should treat this complication, which is often associated with a poor prognosis. This is the first case report to suggest a pathogenetic relationship between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis. The link between ANCA-associated systemic vasculitis and aPAP-related pulmonary fibrosis must be explored with further research.

Consent

Because the patient passed away due to the progression of respiratory failure, written informed consent was obtained from the patient's wife for publication of this case report and any accompanying images. A copy is available for review by the Editor of this journal.

Abbreviations

aPAP: Autoimmune pulmonary alveolar proteinosis; GM-CSF: Granulocyte-macrophage colony stimulating factor; HRCT: High-resolution computed tomography; BALF: Broncho-alveolar lavage fluid; MPO: Myeloperoxidase; ANCA: Anti-neutrophil cytoplasmic antibody; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YK, HK, and YI analyzed and interpreted the patient's data and drafted the manuscript. MH performed the ELISA for anti-GM-CSF antibody. AN, YT, YH, KF, HH, KI, TM, IN, YT, TF, TK, and AK revised the clinical data and supervised drafting of the case report. All authors read and approved the final manuscript.

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References

1. Sakagami T, Uchida K, Suzuki T, Carey BC, Wood RE, Wert SE, Whitsett JA, Trapnell BC, Luisetti M: **Human GM-CSF autoantibodies and reproduction of pulmonary alveolar proteinosis.** *N Engl J Med* 2009, **361**:2679–2681.
2. Inoue Y, Trapnell BC, Tazawa R, Arai T, Takada T, Hizawa N, Kasahara Y, Tatsumi K, Hojo M, Ichiwata T, Tanaka N, Yamaguchi E, Eda R, Oishi K, Tsuchihashi Y, Kaneko C, Nukiwa T, Sakatani M, Krischer JP, Nakata K, Japanese Center of the Rare Lung Diseases Consortium: **Characteristics of a Large Cohort of Patients with Autoimmune Pulmonary Alveolar Proteinosis in Japan.** *Am J Respir Crit Care Med* 2008, **177**:752–762.
3. Hudson AR, Halprin GM, Miller JA, Kilburn KH: **Pulmonary interstitial fibrosis following alveolar proteinosis.** *Chest* 1974, **65**:700–702.
4. Miller PA, Ravin CE, Walker Smith GJ, Osborne DR: **Pulmonary alveolar proteinosis with interstitial involvement.** *Am J Roentgenol* 1981, **137**:1069–1071.
5. Arbiser ZK, Guidot DM, Pine JR, Giltman LI, Gal AA: **Pulmonary alveolar proteinosis mimicking idiopathic pulmonary fibrosis.** *Ann Diag Pathol* 2003, **7**:82–86.
6. Chroneou A, Zias N, Tronic BS, Gonzalez AV, Beamis JF Jr: **A case of uncomplicated pulmonary alveolar proteinosis evolving to pulmonary fibrosis.** *Monaldi Arch Chest Dis* 2007, **67**:234–237.
7. Luisetti M, Bruno P, Kadija Z, Suzuki T, Raffa S, Torrisi MR, Campo I, Mariani F, Pozzi E, Trapnell BC, Mariotta S: **Relationship between diffuse pulmonary fibrosis, alveolar proteinosis, and granulocyte-macrophage colony stimulating factor autoantibodies.** *Respir Care* 2011, **56**:1608–1610.
8. Xing Z, Ohkawara Y, Jordana M, Graham F, Gauldie J: **Transfer of granulocyte-macrophage colony-stimulating factor gene to rat lung induces eosinophilia, monocytosis, and fibrotic reactions.** *J Clin Invest* 1996, **97**:1102–1110.
9. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR: **The role of antineutrophil cytoplasmic antibody testing in the diagnosis of Wegener granulomatosis.** *Ann Intern Med* 1995, **123**:925–932.
10. Wilk A: **Rational use of ANCA in the diagnosis of vasculitis.** *Rheumatology (Oxf)* 2002, **41**:481–483.
11. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, Mahr A, Segelmark M, Cohen-Tervaert JW, Scott D: **Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies.** *Ann Rheum Dis* 2007, **66**:222–227.
12. Kallenberg CGM, Heeringa P, Stegeman CA: **Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides.** *Nat Clin Pract Rheumatol* 2006, **2**:661–670.
13. Ito-Ihara T, Muso E, Kobayashi S, Uno K, Tamura N, Yamanishi Y, Fukatsu A, Watts RA, Scott DG, Jayne DR, Suzuki K, Hashimoto H: **A comparative study of the diagnostic accuracy of ELISA systems for the detection of anti-neutrophil cytoplasmic antibodies available in Japan and Europe.** *Clin Exp Rheumatol* 2008, **26**:1027–1033.
14. Basu N, Watts R, Bajema I, Baslund B, Bley T, Boers M, Brogan P, Calabrese L, Cid MC, Cohen-Tervaert JW, Flores-Suarez LF, Fujimoto S, de Groot K, Guillevin L, Hatemi G, Hauser T, Jayne D, Jennette C, Kallenberg CG, Kobayashi S, Little MA, Mahr A, McLaren J, Merkel PA, Ozen S, Puechal X, Rasmussen N, Salama A, Salvarani C, Savage C, *et al*: **EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis.** *Ann Rheum Dis* 2010, **69**:1744–1750.
15. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U, RAVE-ITN Research Group: **Rituximab versus cyclophosphamide for ANCA-associated vasculitis.** *N Engl J Med* 2010, **363**:221–232.
16. Shan SK, Phan NB, Goyal G, Sharma G: **Pulmonary alveolar proteinosis in a 67-year-old woman with Wegener's granulomatosis.** *J Gen Intern Med* 2010, **25**:1105–1108.
17. Selmi C, Lu Q, Humble MC: **Heritability versus the role of the environment in autoimmunity.** *J Autoimmun* 2012, **39**:249–252.
18. Rojas-Villarraga A, Amaya J, Rodriguez A, Mantilla RD, Anaya JM: **Introducing polyautoimmunity: secondary autoimmune diseases no longer exist.** *Autoimmune Dis* 2012, **1**:1–9.
19. Seymour JF, Presneill JJ: **Pulmonary alveolar proteinosis: progress in the first 44 years.** *Am J Respir Crit Care Med* 2002, **166**:215–235.
20. Yashiro M, Muso E, Ito-Ihara T, Oyama A, Hashimoto K, Kawamura T, Ono T, Sasayama S: **Significantly high regional morbidity of MPO-ANCA-related angiitis and/or nephritis with respiratory tract involvement after the 1995 great earthquake in Kobe (Japan).** *Am J Kidney Dis* 2000, **35**:889–895.

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Effects of Remifentanil on In-Hospital Mortality and Length of Stay Following Clipping of Intracranial Aneurysm: A Propensity Score-matched Analysis

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Background: Remifentanil is an ultrashort-acting μ-opioid receptor agonist and is especially suitable for neuroanesthesia. We previously reported that general anesthesia with remifentanil for brain tumor resection was associated with lower postoperative mortality and shorter postoperative length of stay (LOS) when compared with surgeries without remifentanil. This phenomenon may also exist during clipping of intracranial aneurysms (ICAs), where brain tissue frequently suffers ischemia and reperfusion injury. We performed a propensity score-matching study to compare in-hospital mortality and postoperative LOS with and without remifentanil in such patients.

Methods: We used the Diagnosis Procedure Combination inpatient database in Japan that includes 926 acute care hospitals to identify patients who underwent clipping of ICAs under general anesthesia between July and December 2007.

Results: Of the 4502 patients who underwent ICA clipping, 1380 propensity-matched pairs (n = 2760) were included for outcome comparison. The remifentanil group had significantly lower in-hospital mortality than the nonremifentanil group (4.2% vs. 7.7%; $P < 0.001$). Use of remifentanil was an independent factor for lower in-hospital mortality (odds ratio = 0.52; 95% confidence interval, 0.37-0.74; $P < 0.001$). By contrast, postoperative LOS did not differ significantly between the 2 groups. There was no difference in the occurrence of postoperative complications except for hydrocephalus, which was more common with remifentanil.

Conclusions: This retrospective observational study demonstrated a possible relationship between the use of remifentanil for neuroanesthesia and reduced mortality of patients undergoing clipping of ICAs with open craniotomy. Prospective interventional studies are necessary to confirm this relationship.

Key Words: remifentanil, clipping of intracranial aneurysm, subarachnoid hemorrhage, postoperative mortality, general anesthesia, Diagnosis Procedure Combination, propensity score matching, large administrative claim database

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Remifentanil, a μ-opioid receptor agonist, has a unique pharmacokinetic profile, including a short half-life.[1] The clinical efficiency of remifentanil is especially recognized in neuroanesthesia, where rapid postoperative emergence is often desirable.[2] Using a Japanese nationwide administrative database,[3] we recently reported that general anesthesia with remifentanil is associated with reduced postoperative mortality as well as shorter postoperative length of stay (LOS) compared with fentanyl alone in patients undergoing brain tumor resection.[4] In patients undergoing rectal cancer surgery with intraoperative epidural anesthesia, the above phenomenon was not observed, possibly indicating that the surgical stress response that can be suppressed by epidural anesthesia may affect postoperative outcome. This response may also be efficiently suppressed by remifentanil in neurosurgery, consequently creating better outcomes.[4]

Ruptured intracranial aneurysm (ICA) constitutes 15% of all cerebrovascular accidents, with an incidence of

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> 700,000 cases per year in the United States.[5] Thirty-day mortality is reported to be approximately 45% in the United States[5] and 34% in Japan[6] and half of the survivors suffer irreversible brain damage.[5] Postoperative neurological deficits are common due to factors such as brain retraction, vessel occlusion, and intraoperative hemorrhage,[7] especially in ruptured ICA.

In our previous report, we included patients without any preoperative changes in consciousness (Japan Coma Scale [JCS] = 0),[8] to exclude those with preoperative brain damage/ischemia that may have affected the postoperative outcome.[7] Until now, it was unknown how general anesthesia with remifentanil affects early postoperative outcomes in patients with increased intracranial pressure.

In the present study, we hypothesized that general anesthesia supplemented with remifentanil works favorably to early postoperative outcome in patients undergoing clipping of ICAs. To address this hypothesis, we retrospectively surveyed a large administrative claims database in Japan and applied propensity score-matched analyses to compare factors related to postoperative outcome between remifentanil and nonremifentanil patients who underwent clipping of ruptured/unruptured ICAs.

METHODS

Data Source

The details of the Diagnosis Procedure Combination (DPC) database have been described previously.[3,4,9] Briefly, the DPC is a Japanese case-mix classification system linked with a lump-sum payment system launched in 2002 by the Ministry of Health, Labour, and Welfare of Japan. All 82 academic hospitals in Japan are obliged to use the DPC system, whereas community hospitals can use it voluntarily. In 2007, 926 hospitals, approximately 3 million patients were enrolled in the system that represents about 45% of all inpatient admissions to acute care hospitals in Japan. A survey of DPC-participating hospitals is conducted between July 1 and December 31 annually by the DPC-Research Group, funded by the Ministry of Health, Labour, and Welfare.[10,11]

The database includes the following information: unique identifier for each hospital; age and sex, diagnoses at admission, comorbidities, in-hospital complications recorded using text data in the Japanese language and the International Classification of Diseases 10th Revision codes; medical procedures coded using original Japanese codes; duration of anesthesia (min); list of drug and the dates when it was used; and LOS and discharge status. The level of consciousness at admission for all patients was evaluated using JCS, which is widely used by Japanese clinical facilities including emergency services for assessment of consciousness level. The JCS and the Glasgow Coma Scale are well correlated.[8]

This study was based on a secondary analysis of administrative claims data. Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board of the Graduate School of Medicine at the University of Tokyo (IRB# 3501).

Patient Selection

From the 3 million inpatients recorded between July 1 and December 31, 2007, we selected patients who underwent clipping of ruptured/unruptured ICA with open craniotomy under general anesthesia. We then selected patients who received fentanyl or remifentanil during general anesthesia and divided them into 2 subgroups: (a) patients who received both remifentanil and fentanyl; and (b) those who received fentanyl alone. We excluded patients who died within 3 days after admission because we suspected that the preoperative brain damage in these patients was so serious that physiological derangement would have occurred, and that this might have led the anesthesia care provider to choose conventional opioids such as fentanyl.[12] Figure 1 shows a diagram illustrating how the patients were included for the analysis.

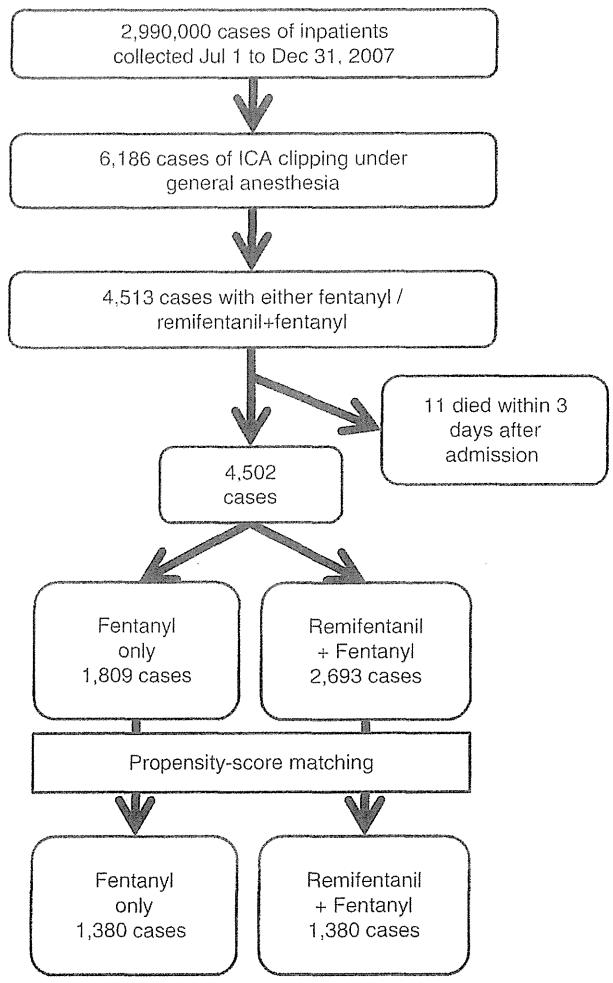

FIGURE 1. Patient inclusions and exclusions. The numbers of patients included/excluded based on each inclusion/exclusion criterion are demonstrated. ICA indicates intracranial aneurysm.

Patient Background Data

Patient background data that could potentially affect the study end points, such as age, sex, and comorbidities, were assessed. The comorbidities were as follows: hypertension, diabetes, chronic heart disease (ischemic heart disease, valvular heart disease, cardiomyopathy, or congenital heart disease), chronic lung disease (emphysema, chronic bronchitis, bronchiectasis, asthma, interstitial lung disease, or pulmonary hypertension), liver cirrhosis, and chronic renal failure. We also evaluated the use of volatile anesthetic agents (sevoflurane, isoflurane, enflurane, or halothane), nitrous oxide, and propofol for each patient. We assessed the type of hospital (academic, nonacademic) and hospital inpatient volumes for ICA clipping, because these factors could potentially affect postoperative outcomes, including mortality.[13] Hospital volumes were determined by the number of ICA clipping procedures performed during the study period, using the unique identifier for each hospital. Numbers of clipping and duration of anesthesia, which may indicate whether surgical difficulties occurred, were included. Use of blood transfusion, which is correlated with intraoperative bleeding, was also included because it affects postoperative outcomes.

For postoperative complications, we extracted postoperative cerebral infarction, cerebrovascular spasm, cerebral hemorrhage, hydrocephalus, pulmonary complications, cardiovascular complications, sepsis, and diffuse intravascular coagulation according to the Japanese text and International Classification of Disease-10 codes in the database.

End Points

The primary end point was in-hospital mortality. Postoperative LOS, postoperative complications including hydrocephalus, brain infarction, and cardiovascular and respiratory complications were assessed as a secondary end point.

Statistical Analysis

As the patients were not randomly assigned to receive remifentanil, we used propensity score matching[11,14] to adjust for differences in baseline characteristics. We applied one-to-one matched analysis on the basis of the estimated propensity scores for each patient. The log odds of the probability that a patient received remifentanil were modeled for potential confounders including age, sex, type of aneurysm (unruptured or ruptured), preoperative consciousness level, number of clippings, preoperative comorbidities (hypertension, diabetes mellitus, chronic lung disease, cardiovascular disease, liver cirrhosis, or chronic renal failure), duration of anesthesia, blood transfusion, type of hospital, and hospital volume. We also included anesthetic agents other than opioids that can affect postoperative recovery, such as nitrous oxide, volatile anesthetics, and propofol. The *C*-statistic for evaluating the goodness of fit was calculated. Each patient who received remifentanil was matched with a patient who did not receive remifentanil with the closest estimated propensity on the logit scale within a specified range (≤ 0.6 of the pooled SD of estimated logits).[11,14]

We compared in-hospital mortality rates and postoperative LOS between the remifentanil and nonremifentanil groups using the χ^2 test and the log-rank test, respectively. The multivariate logistic regression model included age, sex, remifentanil use, and other covariates used for propensity score matching, while also adjusting for clustering of patients within hospitals using a generalized estimating equation.[15]

We compared the proportion of patients discharged from hospital between the subgroups in each covariate using the Kaplan-Meier method and log-rank tests. Cox proportional hazards regression analysis was performed to model the concurrent effects of various factors on the proportion of patients discharged, including age, sex, remifentanil use, and other covariates used for propensity score matching.

We presented odds ratios and 95% confidence intervals (95% CIs) for the logistic regressions and hazard ratios and 95% CIs for the Cox regressions. The threshold for significance was $P < 0.05$. All statistical analyses were conducted using IBM SPSS version 19.0 (IBM SPSS, Armonk, NY).

RESULTS

Of the 3 million inpatients, we identified 6186 ICA clipping procedures performed between July and December, 2007. After inclusion of patients who were administered either fentanyl or remifentanil, we selected 4502 patients who underwent clipping of unruptured or ruptured ICAs under general anesthesia (2693 with both remifentanil and fentanyl and 1809 with fentanyl alone) (Table 1). Using one-to-one propensity score matching, we selected 1380 pairs from the remifentanil and nonremifentanil groups. The *C*-statistic was calculated to be 0.733.

Table 1 shows background data for patients in the remifentanil and nonremifentanil groups who underwent ICA clipping, before and after propensity score matching. Remifentanil was more likely to be used in patients with an unruptured ICA, those with longer duration of anesthesia, and those treated in academic hospitals. Mean hospital volume for clipping was higher in the remifentanil group. Remifentanil was less likely to be used in patients with cardiovascular disease. Before propensity score matching, the proportions of remifentanil patients receiving nitrous oxide or volatile agents were significantly lower than those of nonremifentanil patients, whereas propofol was more frequently used in the remifentanil group than in the nonremifentanil group. After propensity score matching, patient distributions were closely balanced between the remifentanil and nonremifentanil groups.

Table 2 shows the results of χ^2 tests for postoperative in-hospital mortality and log-rank tests for postoperative LOS comparing the remifentanil and nonremifentanil groups. There was a significant difference in in-hospital mortality between the 2 groups (4.2% vs.

TABLE 1. Patient Backgrounds and Use of Volatile Agents

	Before Propensity Score Matching			After Propensity Score Matching		
	Remifentanil and Fentanyl (n = 2693)	Fentanyl Alone (n = 1809)	*P*	Remifentanil and Fentanyl (n = 1380)	Fentanyl Alone (n = 1380)	*P*
Patient background						
Age (mean ± SD)	61.2 ± 11.8	61.8 ± 12.3	0.115	61.7 ± 11.9	61.6 ± 12.3	0.786
Sex (male) (n [%])	915 (34.0)	611 (33.8)	0.889	491 (35.6)	465 (33.7)	0.298
Diagnosis and consciousness level (n [%])						
Unruptured ICA	1289 (47.9)	665 (36.8)	< 0.001	552 (40.0)	538 (39.0)	0.484
Ruptured ICA with JCS grade 0	416 (15.4)	299 (16.5)		232 (16.8)	213 (15.4)	
Ruptured ICA with JCS grade 1	391 (14.5)	334 (18.5)		234 (17.0)	229 (16.6)	
Ruptured ICA with JCS grade 2	294 (10.9)	239 (13.2)		176 (12.8)	184 (13.3)	
Ruptured ICA with JCS grade 3	303 (11.3)	272 (15.0)		186 (13.5)	216 (15.7)	
No. clippings						
1	2277 (86.3)	1561 (84.6)	0.104	1175 (85.1)	1182 (85.7)	0.706
≥ 2	416 (15.4)	248 (13.7)		205 (14.9)	198 (14.3)	
Comorbidities (n [%])						
Hypertension	783 (29.1)	502 (27.8)	0.334	409 (29.6)	396 (28.7)	0.586
Diabetes	121 (4.5)	66 (3.6)	0.164	53 (3.8)	52 (3.8)	0.921
Cardiovascular diseases	78 (2.9)	73 (4.0)	0.037	53 (3.8)	57 (4.1)	0.697
Chronic lung diseases	88 (3.3)	43 (2.4)	0.081	42 (3.0)	39 (2.8)	0.735
Liver cirrhosis	3 (0.1)	2 (0.1)	0.993	2 (0.1)	2 (0.1)	1.000
Chronic renal failure	14 (0.5)	18 (1.0)	0.063	7 (0.5)	12 (0.9)	0.250
Duration of anesthesia (mean ± SD) (h)	6.1 ± 2.4	5.8 ± 2.1	< 0.001	5.9 ± 2.3	5.9 ± 2.2	0.907
Blood transfusion (yes [%])	276 (10.2)	212 (11.7)	0.120	150 (10.9)	160 (11.6)	0.547
Academic hospital (n [%])	647 (24.0)	168 (9.3)	< 0.001	141 (10.2)	162 (11.7)	0.201
Hospital volume for clipping surgery (per 6 mo [mean ± SD])	35.1 ± 49.1	27.1 ± 28.0	< 0.001	27.8 ± 37.9	29.0 ± 30.4	0.366
Use of other anesthetics (n [%])						
Nitrous oxide	264 (9.8)	507 (28.0)	< 0.001	238 (17.2)	271 (19.6)	0.105
Volatile agents	1884 (70.0)	1627 (89.9)	< 0.001	1183 (85.7)	1212 (87.8)	0.103
Propofol	2460 (91.3)	1477 (81.6)	< 0.001	1186 (85.9)	1180 (85.5)	0.744

ICA indicates intracranial aneurysm; JCS, Japan Coma Scale.

7.7%; $P < 0.001$). This phenomenon was observed in patients with ruptured ICAs with worse preoperative level of consciousness (ie, JCS Grade 3). Only 1 in-hospital death occurred among the patients with unruptured ICAs. Postoperative LOS was not significantly different between the 2 groups. The occurrence of postoperative neurological, cardiovascular, pulmonary, and infectious complications did not differ significantly between the

TABLE 2. Comparison of In-Hospital Death and Postoperative Complications by χ^2 Test and Comparison of Postoperative Length of Stay by Log-Rank Test

	Remifentanil and Fentanyl (n = 1380)	Fentanyl Alone (n = 1380)	*P*
In-hospital death (n [%])			
Overall	58 (4.2)	106 (7.7)	< 0.001
Diagnosis and consciousness level			
Ruptured ICA with JCS grade 0	3/232 (1.3)	11/213 (5.2)	0.019
Ruptured ICA with JCS grade 1	19/234 (8.1)	20/229 (8.1)	0.812
Ruptured ICA with JCS grade 2	14/176 (8.0)	25/184 (13.6)	0.086
Ruptured ICA with JCS grade 3	22/186 (11.8)	49/216 (22.7)	0.004
Unruptured ICA	0/552 (0)	1/538 (0.2)	0.311
Postoperative LOS (mean [95% CI]) (d)	37.7 (35.9-39.4)	36.7 (34.9-38.4)	0.433
Postoperative complications (n [%])			
Cerebral infarction	93 (6.7)	113 (8.2)	0.147
Cerebrovascular spasm	117 (8.5)	112 (8.1)	0.730
Cerebral hemorrhage	13 (0.9)	10 (0.7)	0.530
Hydrochephalus	185 (13.4)	150 (10.9)	0.041
Pulmonary complications	90 (6.5)	101 (7.3)	0.409
Cardiovascular complications	23 (1.7)	24 (1.7)	0.883
Sepsis, DIC	17 (1.2)	19 (1.4)	0.737
Postoperative LOS (mean [95% CI]) (d)	37.7 (35.9-39.4)	36.7 (34.9-38.4)	0.433

CI indicates confidence interval; DIC, disseminated intravascular coagulation; ICA, intracranial aneurysm; JCS, Japan Coma Scale; LOS, length of stay.

groups except for hydrocephalus, which was more common in the remifentanil group.

Table 3 shows the results of logistic generalized estimating equation regression analysis of in-hospital mortality following ICA clipping. The remifentanil group had a significantly lower mortality than the nonremifentanil group (odds ratio = 0.52; 95% CI, 0.37-0.74; $P < 0.001$). Greater age and male sex were significantly associated with higher mortality. Worse preoperative consciousness level and intraoperative blood transfusion were also associated with higher in-hospital mortality. Academic hospital and preoperative hypertension were associated with lower mortality. Number of clippings, duration of anesthesia, and hospital volume were not significant predictors for in-hospital mortality. Use of other anesthetic agents including propofol, nitrous oxide, and volatile agents was not significantly associated with in-hospital mortality.

Table 4 shows the results of Cox proportional hazards regression analysis of the proportion of patients discharged from hospital following ICA clipping. Greater age, male sex, diabetes, cardiac disease, chronic renal failure, intraoperative blood transfusion, and longer duration of anesthesia were significantly associated with a lower proportion of discharge. Better preoperative consciousness level and treatment in an academic or high-volume hospital were significantly associated with the higher proportion of discharge. Use of anesthetic agents including remifentanil was not significantly associated with the proportion of patients discharged.

TABLE 3. Logistic Regression Analysis of In-Hospital Mortality

	OR	95% CI	P
Age (y)			
≤49	Reference		
50-59	1.27	0.71-2.28	0.421
60-69	1.64	0.90-2.99	0.105
70-79	1.75	0.94-3.25	0.077
≥80	2.58	1.25-5.32	0.01
Sex			
Male	Reference		
Female	0.61	0.43-0.86	0.004
Comorbidities			
Hypertension	0.65	0.43-0.97	0.035
Diabetes	1.17	0.48-2.85	0.733
Cardiac disease	1.47	0.61-3.56	0.397
Chronic lung disease	1.67	0.87-3.19	0.122
Liver cirrhosis	2.39	0.36-16.00	0.367
Chronic renal failure	2.05	0.56-7.54	0.278
Diagnosis and consciousness level			
Unruptured ICA	0.03	0.01-0.25	0.001
Ruptured ICA with JCS grade 0	Reference		
Ruptured ICA with JCS grade 1	2.85	1.53-5.31	0.001
Ruptured ICA with JCS grade 2	3.53	1.85-6.72	< 0.001
Ruptured ICA with JCS grade 3	5.79	2.98-11.25	< 0.001
Blood transfusion			
No	Reference		
Yes	2.50	1.67-3.75	< 0.001
No. clippings			
1	Reference		
≥2	1.03	0.60-1.77	0.919
Type of hospital			
Nonacademic	Reference		
Academic	0.53	0.29-0.96	0.035
Duration of anesthesia (h)	1.00	1.00-1.00	0.616
Hospital volume (/y)	0.99	0.98-1.00	0.159
Anesthetic agent used			
Fentanyl alone	Reference		
Remifentanil and fentanyl	0.52	0.37-0.74	< 0.001
Nitrous oxide	0.88	0.55-1.41	0.595
Volatile agent	0.70	0.41-1.20	0.200
Propofol	1.12	0.69-1.80	0.655

CI indicates confidence interval; ICA, Intracranial aneurysm; JCS, Japan Coma Scale; OR, odds ratio.

TABLE 4. Cox Regression Analysis of Hospital Discharge

	HR	95% CI	P
Age (y)			
≤49	Reference		
50-59	0.87	0.76-0.98	0.028
60-69	0.72	0.63-0.81	< 0.001
70-79	0.56	0.49-0.64	< 0.001
≥80	0.47	0.38-0.60	< 0.001
Sex			
Male	Reference		
Female	1.10	1.01-1.20	0.024
Comorbidities			
Hypertension	1.00	0.92-1.09	0.968
Diabetes	0.70	0.57-0.87	0.001
Cardiac disease	0.81	0.66-0.99	0.039
Chronic lung disease	0.82	0.64-1.05	0.114
Liver cirrhosis	1.45	0.47-4.54	0.520
Chronic renal failure	0.36	0.21-0.61	< 0.001
Diagnosis and consciousness level			
Unruptured ICA	3.13	2.78-3.52	< 0.001
Ruptured ICA with JCS grade 0	Reference		
Ruptured ICA with JCS grade 1	0.74	0.65-0.85	< 0.001
Ruptured ICA with JCS grade 2	0.63	0.54-0.73	< 0.001
Ruptured ICA with JCS grade 3	0.44	0.38-0.51	< 0.001
Blood transfusion			
No	Reference		
Yes	0.65	0.57-0.75	< 0.001
No. clippings			
1	Reference		
≥2	0.90	0.81-1.01	0.069
Type of hospital			
Nonacademic	Reference		
Academic	1.30	1.15-1.47	< 0.001
Duration of anesthesia (h)	0.91	0.90-0.93	< 0.001
Hospital volume (/y)	1.003	1.001-1.004	< 0.001
Anesthetic agent used			
Fentanyl alone	Reference		
Remifentanil and fentanyl	1.06	0.98-1.14	0.163
Nitrous oxide	1.01	0.91-1.12	0.885
Volatile agent	0.81	0.72-0.91	0.885
Propofol	0.91	0.82-1.02	0.120

CI indicates confidence interval; HR, hazard ratio; ICA, Intracranial aneurysm; JCS, Japan Coma Scale.

DISCUSSION

On propensity score-matched analysis, patients who underwent ICA clipping under general anesthesia with remifentanil had significantly lower in-hospital mortality than those anesthetized without remifentanil, but there was no significant difference in postoperative LOS, or the incidence of postoperative neurological, cardiovascular,