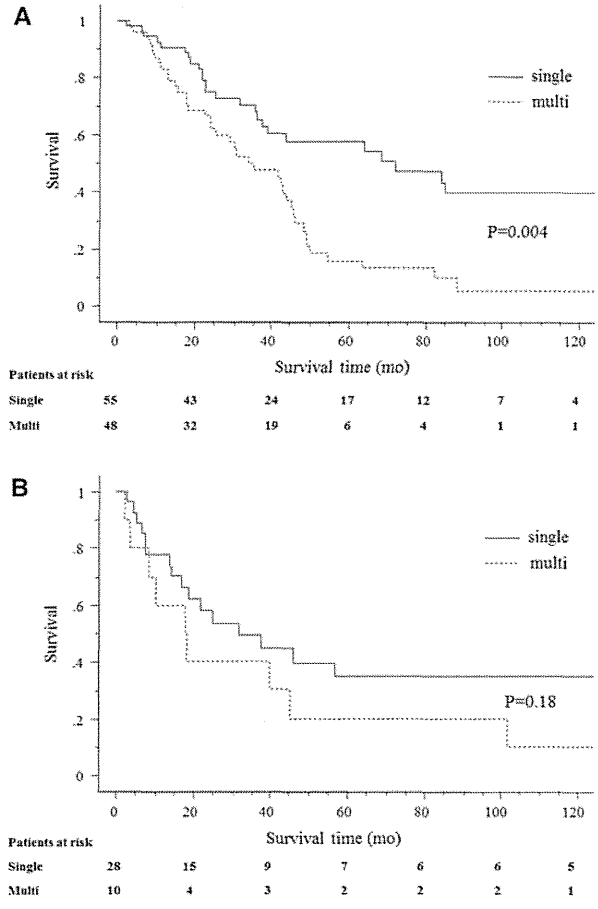

Fig. 2 Survival rate of patients with pathologic N2 according to metastatic N2 levels. Adenocarcinoma patients with single-level N2 had a significantly better survival rate than those with multi-level N2 ($P = 0.004$) (**a**), although this was not the case for patients with squamous cell carcinoma ($P = 0.18$) (**b**)

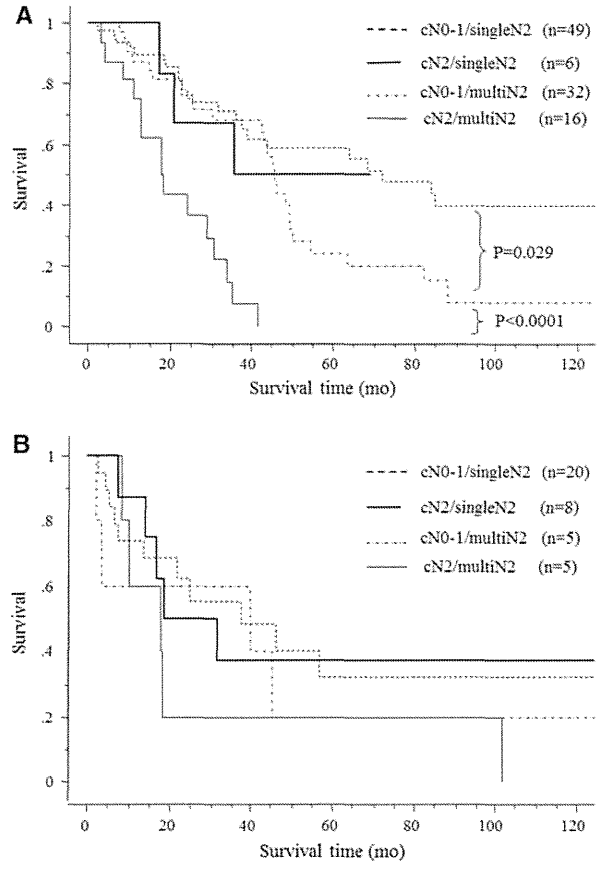

Fig. 3 Survival rate of patients according to clinical N status and metastatic N2 levels. Patients with pathologic N2 were divided into 4 subgroups with different prognoses (**a**). Conversely, the prognosis was similar in squamous cell carcinoma patients regardless of clinical N status or metastatic N2 level (**b**)

Conversely, the prognosis was similar in squamous cell carcinoma patients regardless of clinical N status or metastatic N2 stations (Fig. 3b).

Discussion

Patients with pathologic N2 NSCLC comprise a heterogeneous group in terms of their prognosis (Ratto et al. 2009; Robinson et al. 2007; Suzuki et al. 1999; Andre et al. 2000, Inoue et al. 2004; Sakao et al. 2010), which stems from multiple adverse factors such as clinical N2, incomplete resection, large tumor size, and number of involved mediastinal lymph nodes. In a previous study, Andre et al. (2000) reported four negative prognostic factors: clinical N2, number of involved mediastinal lymph nodes, pathologic T3-4, and lack of preoperative chemotherapy. Vansteenkiste et al. (1997) also noted that survival was poor in patients with higher T status, lower performance status, involvement of multi-station N2, non-squamous histology, and clinical N2. However, few have considered whether the prognosis of patients with pathologic N2 depends on tumor histology.

Clinical N status is one of the most significant prognostic factors in surgically resected N2 NSCLC (Suzuki et al. 1999; Andre et al. 2000). Occult N2 (preoperatively undetectable N2; clinical N0-1) and clinical N2 are two distinct stages of NSCLC (Andre et al. 2000). In the study by Andre et al. (2000), the 5-year survival rates of patients with pathologic N2 were 29, and 7% for clinical N0-1 and clinical N2 patients, respectively. As many as one quarter of patients with pathologic N2 are found in surgery to have occult N2 metastatic disease (Goldstraw et al. 1994; Misthos et al.2004). The prognosis of patients with occult N2 metastasis (clinical N0-1) is better than for patients with clinical N2. Thus, patients with incidental N2 at surgery have the best chance of survival (Andre et al.2000;

Goldstraw et al. 1994). In the present study, however, clinical N status was a significant prognostic factor only in patients with pathologic N2 adenocarcinoma. Thus, clinical N0-1 indicates a better prognosis than clinical N2 only in adenocarcinoma patients, and not in squamous cell carcinoma patients.

It has been shown that multi-station N2 patients have much poorer prognoses than those with single-station N2 (Andre et al. 2000; Goldstraw et al. 1994), although Keller et al. (2004) documented that this was the case only where the tumor was detected in the left upper lobe. Ichinose et al. (2001) also reported that single-station N2 is a good prognostic factor except for patients with a primary tumor in the left lower lobe. Misthos et al. (2008) reported that skip metastasis, regional N2 spread, and single-station N2 all correlated with good survival rates, although multivariate analysis established single-station N2 as the only independent favorable prognostic factor. Patients with the involvement of single-station N2 fared significantly better than patients with multi-station N2 (Ratto et al. 2009; Inoue et al. 2004; Misthos et al. 2008). Andre et al. (2000) also reported that the number of involved mediastinal lymph node levels was an independent prognostic factor. In this study, multi-station N2 was a significant prognostic factor only for patients with pathologic N2 adenocarcinoma, not for squamous cell carcinoma patients. Squamous cell carcinoma patients with pathologic N2 had a similar prognosis even if they had clinical N0-1 or single-station N2.

A preoperative N2 status and the number of involved lymph node stations are the most relevant prognostic factors in N2 NSCLC (Andre et al. 2000). Sakao et al. (2010) also reported that among patients with multi-station N2, the prognoses were different between those with clinical N0-1 and those with clinical N2. Andre et al. (2000) stated that surgery was mandatory in patients with clinical N0-1 and single-station N2. In this study, multivariate analyses indicated that clinical N2, incomplete resection, and multi-station N2 were significant prognostic factors for patients with adenocarcinoma. In adenocarcinoma, patients can be classified into 4 distinct prognostic subgroups according to clinical N status and metastasis N2 stations. Clinical N status and metastasis N2 stations were associated with prognosis in adenocarcinoma. In our study, the 5-year survival rate of adenocarcinoma patients with clinical N0-1 and single-station N2 was relatively good: 58.8%. On the contrary, in squamous cell carcinoma, it is interesting that patients cannot be classified into these subgroups. The prognosis was similar in squamous cell carcinoma patients regardless of clinical N status or metastatic N2 stations. This result may be due to the different metastatic properties of the two tumor histologies. We supposed that patients who discovered surgically positive N2 nodes or those with single-station N2 in adenocarcinoma patients could benefit from surgical resection. On the contrary, surgery was not beneficial to patients with both clinical N2 and multi-station N2 in either histologic subgroup.

Limitations of this study, however, are that the analysis was retrospective and that the exclusion of unresectable N2 led to a bias in the subclassification. In addition, routine adjuvant chemotherapy for N2 patients was started in 2005. Therefore, it was difficult to evaluate the effect of adjuvant chemotherapy on prognosis in this study. Furthermore, the sample of patients with N2, especially that of squamous cell carcinoma patients, was small, which restricted our ability to generalize the results. A greater number of patients with N2 should be investigated further in future studies to determine the prognostic heterogeneity of tumor histology. Finally, irrespective of prior CT or PET scan finding, transbronchial or endobronchial ultrasound fine needle aspiration for mediastinal small lymph nodes was warranted, which might have a substantial impact on further management.

In conclusion, adenocarcinoma patients can be grouped according to their prognoses by clinical N status and metastatic N2 stations. This was not the case in squamous cell carcinoma. Tumor histology affects the prognostic factors of patients with pathologic N2 NSCLC.

Conflict of interest None declared.

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ORIGINAL ARTICLE

Effects of low-dose human atrial natriuretic peptide for preventing post-operative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer

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Abstract

OBJECTIVES: The objective of the present study was to evaluate the clinical effects of human atrial natriuretic peptide (hANP) on post-operative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer.

METHODS: A retrospective study involving 44 consecutive patients aged ≥75 years who had elevated pre-operative B-type natriuretic peptide levels (≥30 pg/ml) and underwent a scheduled pulmonary resection for lung cancer in two specialized thoracic centres between April 2008 and March 2010. Results were compared between the patients who did and did not receive hANP during the peri-operative period. The primary endpoint was the incidence of post-operative cardiopulmonary complications. Post-operative haemodynamics, white blood cell (WBC) counts and C-reactive protein (CRP) levels were also examined.

RESULTS: The incidence of post-operative cardiopulmonary complications was significantly lower in the hANP group than that in the control group (26 vs. 86%, $P < 0.0001$). Patients in the hANP group showed significantly lower WBC counts and serum CRP levels post-operatively.

CONCLUSIONS: Continuous infusion of low-dose hANP during lung cancer surgery had a prophylactic effect on post-operative cardiopulmonary complications in elderly lung cancer patients.
(Trial registration number: JPRN-UMIN000003631).

Keywords: Lung cancer surgery • Perioperative care • Post-operative complications

INTRODUCTION

Lung cancer is generally a disease of older adults, and age has been shown to be an important risk factor for morbidity and mortality after pulmonary resection [1, 2]. Because of these risks, elderly patients have less chance of undergoing curative surgery than younger patients [3, 4]. However, it is inappropriate that elderly patients undergo limited resections solely because of their advanced age. Since no prophylactic strategy has been established, the development of effective treatment for post-operative morbidity is desirable.

Human atrial natriuretic peptide (hANP) consists of 28 amino acids and has a variety of biological effects when used to treat heart failure. It is now known that hANP exhibits a wide range of cardioprotective effects, including anti-fibrosis, anti-hypertrophy, anti-inflammatory and inhibition of sympathetic nerve activity, the renin-angiotensin-aldosterone system and endothelin synthesis [5, 6]. Post-operative cardiopulmonary complications are often due to haemodynamic, neurohormonal and inflammatory changes in the cardiopulmonary interaction. Since the hANP has beneficial effects on haemodynamics, neurohormonal balance and inflammatory changes [7–10], it is reasonable to expect that the hANP would protect against post-operative cardiopulmonary complications.

Serum B-type natriuretic peptide (BNP) levels, even in a healthy population, increase with age and any comorbidities [11, 12], but it has not been established that elderly patients with mildly elevated BNP levels need to be treated. We previously reported that patients in all age groups with elevated pre-operative BNP levels have an increased risk of developing post-operative atrial fibrillation [13], and elderly patients with elevated pre-operative BNP levels have an increased risk of developing post-operative cardiopulmonary complications following pulmonary resection for lung cancer [14]. The present study aimed to examine the effects of the hANP on post-operative cardiopulmonary complications in such high-risk elderly patients.

MATERIALS AND METHODS

Study design and population

Of the 448 patients who underwent an elective pulmonary resection procedure for lung cancer at Osaka University Graduate School of Medicine and National Toneyama Hospital from April 2008 to March 2010, 56 consecutive elderly patients (≥75 years old) with a pre-operative BNP level of ≥30 pg/ml were included in this open-label, non-randomized and retrospective surveillance study. The cut-off value of BNP (30 pg/ml) was selected based on our previous results [14], showing that this cut-off value of pre-operative BNP can predict the incidence of post-operative cardiopulmonary complications with high sensitivity and specificity in elderly patients undergoing pulmonary resection for lung cancer. Twelve patients were excluded and the exclusion criteria for the present analysis were cardiac rhythm other than sinus, previous atrial fibrillation, antiarrhythmic drug use, thyroid dysfunction, renal failure requiring haemodialysis and repeated pulmonary resection. Thus, 44 patients were finally enrolled. This study population included partially our previous study population [14]. The results of the patients who did and did not receive low-dose hANP were compared. In the hANP group, the subjects received i.v. hANP just before the induction of systemic anaesthesia (0.025 μg/kg/min without a bolus, Daiichisankyo Pharmaceutical Inc., Tokyo, Japan) for 3 days. Complete preoperative and follow-up data were obtained in all of these patients. The study protocol was approved by the Institutional Review Boards of both institutions, and all patients provided written informed consent before participation (trial registration number: JPRN-UMIN000003631).

Surgical procedure

All patients underwent anterolateral thoracotomy or video-assisted thoracic surgery (VATS). We selected the patients with tumour size of ≤3–4 cm and no lymphadenopathy diagnosed using computed tomography for VATS. In VATS, three access ports were placed through 1–2 cm axillary skin incisions. One of these incisions was extended by 4–5 cm, and the resected lung lobe was removed in a plastic bag without using a rib spreader. Patients requiring conversion from VATS to thoracotomy were classified as open thoracotomy patients due to the operative invasiveness, which might affect post-operative complications. All patients received pre-operative epidural anaesthesia for pain management, which usually remained in place for 2–4 days or until the chest drainage tubes were removed, after which they were switched to oral analgesia. Other post-operative management included early ambulation and low-flow nasal oxygen supplementation, as necessary.

Measurements

Pre-operative evaluations included a detailed history and physical examination, blood gas analysis, 12-lead electrocardiogram, spirometry and determination of serum BNP levels. None of the patients had symptomatic coronary artery disease or congestive heart failure. Physical examinations and electrocardiographic findings at rest were unremarkable in the study population. The C-reactive protein (CRP) levels and white blood cell (WBC) counts were determined before surgery and on Days 1, 3 and 7, and 1 month after surgery. The serum BNP concentrations were determined using a chemiluminescence enzyme immunoassay (MI02 Shionogi BNP, Shionogi Pharmaceutical, Osaka, Japan). Haemodynamic parameters, such as systolic blood pressure, diastolic blood pressure, heart rate and urine volume, were recorded before surgery and for the first 4 days after surgery.

Post-operative complications

All patients were followed-up after surgery, and complications occurring during the same hospitalization as the index procedure were recorded. Cardiopulmonary complications were defined as described previously [14] and included respiratory complications such as pneumonia (fever >38°C, purulent sputum, abnormal findings on chest X-ray), acute respiratory distress syndrome [partial pressure of oxygen in arterial blood (PaO_2)/fraction of inspired oxygen (FiO_2) <200 mmHg], respiratory insufficiency requiring tracheostomy, respiratory failure requiring mechanical ventilation, atelectasis with bronchoscopic intervention, initiation of home oxygen treatment and cardiovascular complications including arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia and ventricular tachycardia), angina pectoris, myocardial infarction, congestive heart failure and thromboembolic events. Surgical factors such as prolonged air leaks and bronchopleural fistulas were excluded. Finally, operative mortality was defined as death within 30 days following surgery.

Statistical analysis

Data are presented as the mean ± SD or as the median with interquartile range. Categorical variables are shown as the percentage of the sample. Comparisons between the two groups were assessed by Student's *t*-tests for normally distributed variables, by the Mann-Whitney *U*-test for non-normally distributed variables and by the χ^2 test for categoric variables. All data were analysed with the SPSS statistical software package (version 11.0; IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered significant.

RESULTS

Subjects

There were no significant differences between the two groups in baseline characteristics, surgical data, use of catecholamines, pre-operative pulmonary function and serum BNP levels (Table 1). In both the groups, most patients had one or more major comorbid conditions, most commonly hypertension. Both the groups had relatively higher pre-operative BNP levels and underwent lobectomies in most cases.

Incidence of post-operative cardiopulmonary complications

Post-operative cardiopulmonary complications were identified in 18 (86%) subjects in the control group and 6 (26%) subjects

Table 1: Patient characteristics and pre-operative pulmonary function variables

Variables	hANP group (n = 23)	Control group (n = 21)	*P*-value
Age (years)	78.9 ± 2.5	79.1 ± 3.5	0.80
Males	15 (65%)	15 (71%)	0.39
Hypertension	15 (65%)	17 (81%)	0.25
Hypercholesterolaemia	11 (48%)	7 (33%)	0.34
Diabetes mellitus	5 (22%)	3 (14%)	0.53
Ischaemic heart disease	9 (39%)	7 (33%)	0.69
Smoking history	13 (57%)	13 (62%)	0.58
Medication			
Calcium channel blockers	8 (35%)	9 (43%)	0.95
β-blockers	1 (4%)	2 (10%)	0.62
ACE inhibitors or ARBs	4 (17%)	5 (24%)	0.83
Statins	3 (13%)	2 (10%)	0.57
Estimated GFR (ml/min/1.73 m^2)	58.8 ± 10	60.5 ± 13	0.78
Procedure			
Wide wedge resection	2 (9%)	1 (5%)	0.62
Segmentectomy	2 (9%)	2 (10%)	0.93
Lobectomy	19 (83%)	18 (86%)	0.78
VATS procedure	12 (52%)	10 (48%)	0.98
Operating time (min)	197 (178–273)	222 (204–263)	0.37
Blood loss (ml)	55.0 (30.0–200)	77.5 (11.2–240)	0.95
Mediastinal lymph node dissection	12 (52%)	7 (33%)	0.22
Use of catecholamines	3 (13%)	4 (19%)	0.60
Lung cancer staging			
IA, IB	15 (65%)	17 (81%)	0.25
IIA, IIB	3 (13%)	1 (5%)	0.35
IIIA, IIIB	5 (22%)	3 (14%)	0.53
VC, % predicted	96.4 ± 12	97.4 ± 16	0.81
FEV_1, % predicted	84.5 ± 11	84.5 ± 18	0.99
FEV_1/FVC, %	76.7 ± 8.0	74.8 ± 12	0.54
DLco, % predicted	94.6 ± 23	94.0 ± 29	0.94
PaO_2, Torr	85.4 ± 11	89.2 ± 15	0.41
$PaCO_2$, Torr	40.5 ± 3.9	39.2 ± 4.2	0.32
BNP, pg/ml	49.6 (33.9–77.2)	46.1 (35.9–82.3)	0.92

Values are shown as numbers (%), means ± SD or the median with interquartile range.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BNP: B-type natriuretic peptide; DLco: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory ventilation in 1 s; FVC: forced vital capacity; GFR: glomerular filtration rate; $PaCO_2$: carbon dioxide blood partial pressure; PaO_2: arterial oxygen blood partial pressure; VATS: video-assisted thoracoscopic surgery; VC: vital capacity.

in the hANP group (Table 2). The incidence of post-operative cardiopulmonary complications was significantly lower in the hANP group ($P < 0.001$). The most common complications in both the groups were arrhythmias, and the incidence of cardiovascular complications was significantly lower in the hANP group ($P < 0.001$). Furthermore, the incidence of respiratory complications was also significantly lower in the hANP group ($P < 0.05$). Of the four patients with post-operative home oxygen therapy, two patients had pneumonia and one patient had acute respiratory distress syndrome in acute phase after surgery.

Operative mortality

Overall operative mortality was 2.3% (one patient). The cause of death was an acute myocardial infarction in a control group patient.

Haemodynamics

There were no significant differences between the groups in systolic blood pressure, diastolic blood pressure, heart rate and urine volume (Fig. 1). None of the subjects received a blood transfusion. None of the subjects had the hANP infusion discontinued due to any side effects.

Post-operative white blood cell and C-reactive protein levels

The hANP group had significantly lower WBC counts and CRP levels compared with the control group on Days 3 and 7, as well as 1 month after surgery (Fig. 2), although the period of hANP infusion was for only 3 days.

DISCUSSION

The present results are the first to show that continuous infusion of low-dose hANP has a prophylactic effect on post-operative cardiopulmonary complications in high-risk elderly patients undergoing pulmonary resection for lung cancer. The infusion of low-dose hANP did not significantly change post-operative haemodynamics and decreased the post-operative WBC and CRP levels, which could suggest attenuation of inflammatory changes associated with the prevention of post-operative cardiopulmonary complications. In the present study, continuous infusion of low-dose hANP was highly tolerable, and no clinically significant adverse effects were observed. The present findings indicate that low-dose hANP administration is a valuable treatment option to prevent post-operative cardiopulmonary complications in high-risk elderly patients undergoing thoracic surgery.

The hANP is considered to have various effects on post-operative cardiopulmonary complications in elderly patients undergoing pulmonary resection. First, it has beneficial effects on haemodynamics and neurohormonal balance. Several studies have shown that infusion of hANP increases stroke volume and decreases pulmonary capillary wedge pressure, improving the haemodynamics and the clinical status in patients with congestive heart failure [7, 15]. However, Sezai *et al.* [16] reported that low-dose hANP infusion (0.02 μg/kg/min) did not significantly change haemodynamics, but reduce renin activity and angiotensin and aldosterone levels, and it prevented post-operative cardiovascular complications after coronary artery bypass grafting [17]. Consistent with this result, there were no significant differences between the low-dose hANP and control groups in post-operative haemodynamics among patients who underwent pulmonary resection. Furthermore, in this study, post-operative complications, both cardiovascular and respiratory, were significantly lower in the hANP group. These results are also compatible with the data in the cardiovascular field [16].

Table 2: Post-operative cardiopulmonary complications

Variables	hANP group (n = 23)	Control group (n = 21)	P-value	Risk ratio	95% CI
All cardiopulmonary complications	6 (26)	18 (86)	<0.001*	0.304	0.150–0.619
Cardiovascular complications	5 (22)	12 (57)	0.002*		
Arrhythmias	5	10			
Acute myocardial infarction	0	2			
Respiratory complications	1 (4)	6 (29)	0.028*		
Pneumonia	0	3			
Acute respiratory distress syndrome	1	2			
Home oxygen therapy	0	4			

CI: confidence interval.
*Significant (P < 0.05).

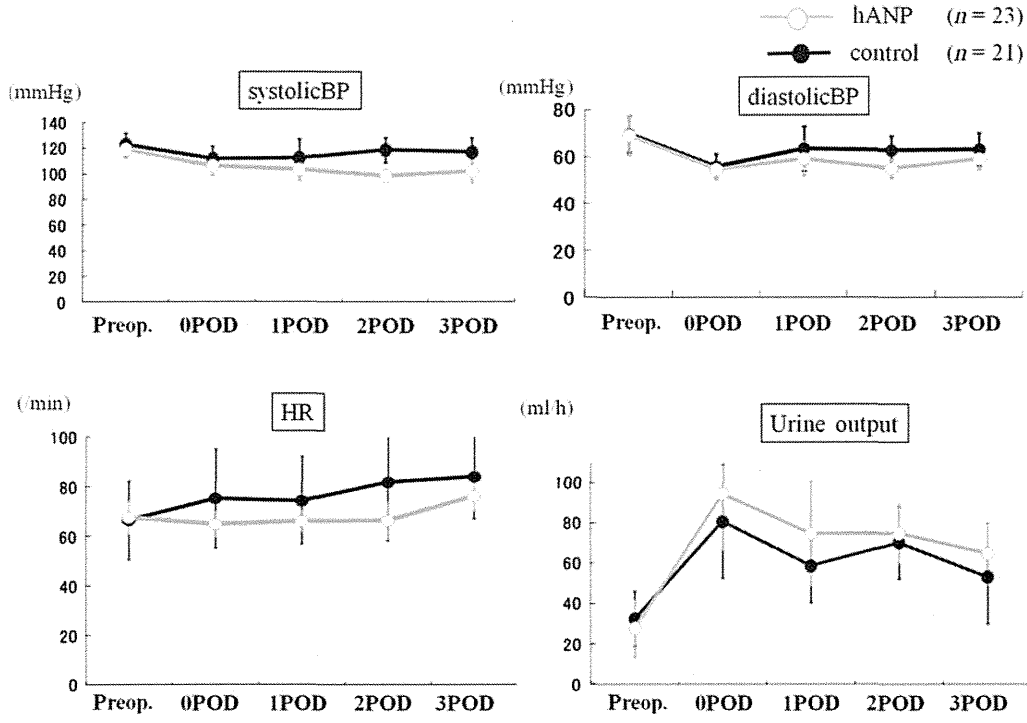

Figure 1: Changes in perioperative systolic blood pressure, diastolic blood pressure, heart rate and urine volume. Each point with bars shows the mean ± SD.

Evidence has recently been presented that atrial natriuretic peptide (ANP) has a much broader range of biological activities, including the inhibition of inflammation and oxidative stress. Several studies have shown that ANP attenuates several pathways of inflammation *in vitro* and *in vivo* model and suggested its role in the regulation of pulmonary function in the setting of acute lung injury and pulmonary inflammation [10, 18]. Xing and Birukova [10] reported that ANP attenuated activation of inflammatory signalling (nuclear factor-kappaB) by lipopolysaccharides and tumour necrosis factor-alpha in human pulmonary endothelial cells. Mitaka *et al.* [18] reported that hANP infusion improved pulmonary gas exchange in patients with acute lung injury during mechanical ventilation. These studies suggest that hANP attenuates systemic inflammatory changes, including pulmonary inflammation, and protects the function of pulmonary endothelial cells after surgery, which might lead to a prophylactic effect for high-risk elderly patients, preventing both cardiovascular and respiratory complications.

Nesiritide, human BNP, is an agent approved for the treatment of symptomatic heart failure in the USA and in some other countries. Recent studies have conflicting conclusions about its effects on renal function [19, 20]. However, Sezai *et al.* [17] recently reported the safety of low-dose hANP with respect to post-operative renal function, and they found that low-dose hANP significantly reduced serum creatine and creatine clearance when compared with placebo after cardiac surgery. In this study, comparison of the estimated glomerular filtration rate

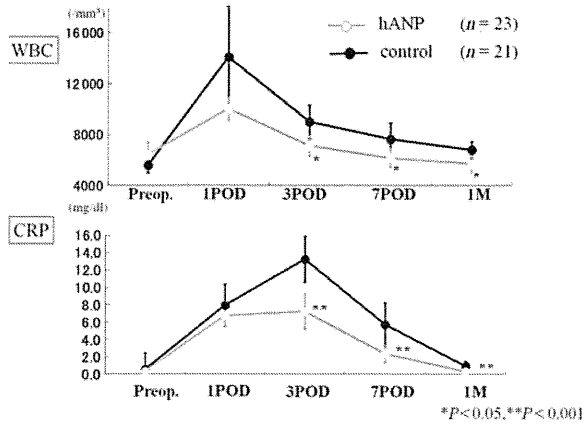

Figure 2: Changes in WBC counts and CRP levels in patients undergoing elective pulmonary resection for lung cancer who did and did not receive hANP. Each point with bars shows the mean ± SD; *$P < 0.05$, **$P < 0.001$.

(GFR) showed no significant difference during the perioperative period, and no patients had an increase in serum creatinine >0.5 mg/dl post-operatively in the hANP group (data not shown). This may be explained by the possibility that low-dose hANP did not significantly change haemodynamics and urine output in this population.

Finally, it is important to note that the hANP group had significantly lower WBC and CRP levels 1 month after surgery than the control group, while the period of hANP infusion was for only 3 days after operation. We believe that the long-term effects and the prognosis, as well as the mechanism of hANP, should be addressed in further studies.

This study was a two-institution clinical study, which restricted our ability to generalize the results. In addition, patients were not assigned to either group randomly. Furthermore, the number of patients in the study cohort was small. Thus, additional investigations with a larger number of patients from multiple institutions are necessary to allow for generalization of the findings obtained here.

The present study is the first to show prophylactic effects of low-dose hANP on post-operative cardiopulmonary complications without major adverse events in high-risk elderly patients undergoing pulmonary resection for lung cancer. Additional studies are warranted to determine whether these effects can be observed in other patients and translated into improved clinical outcomes.

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Conflict of interest: none declared.

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ORIGINAL ARTICLE

THORACIC

Low-dose human atrial natriuretic peptide for the prevention of postoperative cardiopulmonary complications in chronic obstructive pulmonary disease patients undergoing lung cancer surgery†

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Abstract

OBJECTIVES: Lung cancer patients with chronic obstructive pulmonary disease are at an increased risk of respiratory and cardiovascular complications after pulmonary resection. The objective of the present study was to evaluate the clinical effects of low-dose human atrial natriuretic peptide (hANP) on postoperative cardiopulmonary complications in untreated chronic obstructive pulmonary disease patients undergoing lung cancer surgery.

METHODS: Of 824 patients who underwent an elective pulmonary resection procedure for lung cancer in two specialized thoracic centres between 2008 and 2011, 202 consecutive patients who had airflow limitation before surgery were included in this retrospective study. The results were compared between patients who did and those who did not receive hANP during the perioperative period. The primary endpoint was the incidence of postoperative cardiopulmonary complications. Postoperative haemodynamics, white blood cell (WBC) counts and C-reactive protein (CRP) levels were also examined. Furthermore, propensity score matching analysis was used to reduce treatment selection bias from patient characteristics.

RESULTS: The incidence of postoperative cardiopulmonary complications was significantly lower in the hANP group than in the control group (14 vs 36%, $P < 0.01$). The propensity score matching analysis confirmed the significantly decreased frequency of postoperative cardiopulmonary complications in the hANP group. Patients in the hANP group showed significantly lower WBC counts and serum CRP levels postoperatively.

CONCLUSIONS: Treatment with hANP during the perioperative period had a prophylactic effect against postoperative cardiopulmonary complications in chronic obstructive pulmonary disease patients undergoing lung cancer surgery.

Trial registration number: JPRN-UMIN000003631.

Keywords: Lung cancer surgery • Perioperative care • Postoperative complications

INTRODUCTION

Lung cancer patients often have chronic obstructive pulmonary disease (COPD), because both conditions are strongly associated with cigarette smoking. A high prevalence of COPD has been reported in patients with a new diagnosis of lung cancer [1, 2]. Since COPD is often underdiagnosed and undertreated [3], a new diagnosis of COPD is often made during the evaluation of patients requiring surgery for lung cancer. Although surgical resection remains the only potentially curative treatment for lung cancer, lung cancer patients with COPD are at high risk of pulmonary resection surgery [4, 5]. Therefore, perioperative management of COPD is an important issue in lung cancer surgery.

Human atrial natriuretic peptide (hANP), a 28 amino-acid peptide hormone synthesized by the cardiac atria, is commercially available in Japan and has been used in the treatment of acute heart failure. hANP has a wide range of cardioprotective effects, including anti-inflammatory and inhibition of sympathetic nervous system activity [6]. Postoperative cardiopulmonary complications are often caused by inflammatory and neurohormonal changes. Since it is now known that hANP has beneficial effects on inflammatory changes and neurohormonal balance [7, 8], it is plausible to expect that hANP would protect against postoperative cardiopulmonary complications.

We previously reported that hANP has a prophylactic effect on postoperative cardiopulmonary complications in elderly

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high-risk patients [9]. However, the effects of hANP for COPD patients have not yet been clear. The objective of this study was to evaluate the effects of hANP on postoperative cardiopulmonary complications in untreated COPD patients undergoing lung cancer surgery.

MATERIALS AND METHODS

Study design and population

Of the 824 patients who underwent an elective pulmonary resection procedure for lung cancer at Osaka University Graduate School of Medicine and National Toneyama Hospital from 2008 to 2011, 250 consecutive COPD patients were included in this retrospective surveillance study. Airflow limitation was assessed by spirometry and was defined as a postbronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) < 0.70. COPD severity was classified using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, which are based on spirometric findings [10]. Spirometry was performed by a trained technician according to the American Thoracic Society/European Respiratory Society guidelines [11]. Patients diagnosed with respiratory disorders other than COPD, such as asthma, were excluded. The exclusion criteria for the present analysis were history of treatment for COPD, cardiac rhythm other than sinus, previous atrial fibrillation, antiarrhythmic drug use, thyroid dysfunction, renal failure requiring haemodialysis, repeated pulmonary resection and recent pneumonia or myocardial infarction (<1 month). As a result, 48 patients were excluded. Thus, 202 patients were finally enrolled. The results for the patients who did and those who did not receive hANP during the perioperative period were compared. We previously reported that hANP had a prophylactic effect against postoperative cardiopulmonary complications for high-risk patients with elevated preoperative B-type natriuretic peptide (BNP) levels [9]. Therefore, we often used hANP therapy for high-risk COPD patients with elevated BNP levels before surgery. In the hANP group, the subjects received hANP (0.025 μg/kg/min without a bolus (Daiichisankyo Pharmaceutical, Inc., Tokyo, Japan)) for 3 days, which was administered intravenously just before the induction of general anaesthesia. Complete preoperative and follow-up

Table 1: Patients' characteristics and preoperative pulmonary function variables[a]

	hANP group (n = 51)	Control group (n = 151)	P-value
Age (years)	73.5 ± 6.5	68.5 ± 9.0	0.0004
Males	45 (88%)	140 (93%)	0.32
Hypertension	39 (77%)	84 (56%)	0.008
Dyslipidaemia	26 (51%)	40 (27%)	0.001
Diabetes mellitus	12 (24%)	26 (17%)	0.32
Ischaemic heart disease	22 (43%)	27 (18%)	0.0002
Smoking history	48 (94%)	144 (95%)	0.73
Medication			
Calcium channel blockers	30 (58%)	78 (52%)	0.42
β-blockers	4 (8%)	5 (3%)	0.18
ACE inhibitors or ARBs	11 (21%)	26 (17%)	0.49
Statins	16 (31%)	28 (19%)	0.06
VATS procedure	25 (49%)	78 (52%)	0.75
Operating time (minutes)	194 (164–251)	215 (179–254)	0.71
Blood loss (ml)	90 (40–250)	100 (50–219)	0.84
Mediastinal lymph node dissection	38 (75%)	113 (75%)	0.96
Use of catecholamines	5 (10%)	18 (12%)	0.68
Surgical procedure			
Pneumonectomy	1 (2%)	3 (2%)	0.99
Lobectomy	42 (82%)	130 (86%)	0.52
Segmentectomy or wedge resection	8 (16%)	18 (12%)	0.49
Lung cancer staging			
IA, IB	40 (78%)	108 (72%)	0.34
IIA, IIB	7 (14%)	25 (17%)	0.63
IIIA, IIIB	4 (8%)	18 (12%)	0.81
VC, % predicted	101 ± 14	106 ± 16	0.07
FEV_1, % predicted	79.8 ± 12	77.0 ± 14	0.25
DLco, % predicted	95.0 ± 23	93.8 ± 23	0.30
PaO_2, Torr	86.6 ± 8.2	86.1 ± 11	0.45
$PaCO_2$, Torr	39.4 ± 5.2	39.8 ± 4.1	0.76
BNP, pg/ml	53.6 (30.8–95.4)	18.8 (10.6–36.1)	<0.0001
COPD-GOLD stages			
I	25 (49%)	77 (51%)	0.81
II	23 (45%)	65 (43%)	0.80
III	3 (6%)	9 (6%)	0.98

[a]Values are shown as numbers (%), means ± SD or medians with an inter-quartile range.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BNP: B-type natriuretic peptide; DLco: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory ventilation in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease; $PaCO_2$: partial pressure of carbon dioxide in the blood; PaO_2: partial pressure of oxygen in arterial blood; VATS: video-assisted thoracoscopic surgery; VC: vital capacity.

data were obtained for all patients. The study protocol was approved by the Institutional Review Boards of both institutions, and all patients provided their written informed consent before participation (trial registration number: JPRN-UMIN000003631). Preoperative evaluations: all the patients underwent pulmonary resections with anterolateral thoracotomy or thoracoscopic surgery, as previously described [12]. White blood cell (WBC) counts and the levels of C-reactive protein (CRP) and BNP were determined before surgery and 1, 3 and 7 days, as well as 1 month, after surgery. All the complications that occurred during the same hospitalization were recorded. Cardiopulmonary complications were defined as previously described [12].

Statistical analysis

Data are presented as means ± standard deviation (SD) or as medians with an inter-quartile range. All the data were analysed using the SPSS statistical software package (version 11.0; IBM Corporation, Armonk, NY, USA). Categorical variables are shown as the percentage of the sample. Comparisons between the two groups were made by Student's *t*-test for normally distributed variables, by the Mann–Whitney *U*-test for non-normally distributed variables and by the χ^2 test for categorical variables. Probability values <0.05 were considered significant.

In addition, we performed a propensity score matching analysis to reduce treatment selection bias for each group (control group and hANP group). The propensity score for each case was calculated using multilogistic analysis, with age, hypertension, dyslipidaemia, ischaemic heart disease, statin use and BNP levels as variables. The patients were selected by matching propensity scores without clinical information regarding the outcome. Statistical calculations were performed using the R statistical software [13].

RESULTS

Subjects

There were a larger number of patients with older age, hypertension, dyslipidaemia and ischaemic heart disease in the hANP

Table 2: Patient characteristics with propensity score matching analysis[a]

	hANP group (n = 43)	Control group (n = 43)	P-value
Age (years)	72.8 ± 6.7	72.9 ± 9.2	0.97
Males	39 (91%)	37 (86%)	0.51
Hypertension	31 (72%)	29 (67%)	0.64
Dyslipidaemia	18 (42%)	21 (49%)	0.52
Diabetes mellitus	10 (23%)	9 (21%)	0.80
Ischaemic heart disease	16 (37%)	18 (42%)	0.66
Smoking history	41 (95%)	39 (91%)	0.40
Medication			
Calcium channel blockers	21 (49%)	26 (61%)	0.28
β-Blockers	3 (7%)	1 (2%)	0.31
ACE inhibitors or ARBs	8 (19%)	8 (19%)	-
Statins	10 (23%)	11 (26%)	0.80
VATS procedure	22 (51%)	29 (67%)	0.13
Operating time (minutes)	195 (152–257)	206 (165–243)	0.45
Blood loss (ml)	85 (40–240)	100 (35–148)	0.19
Mediastinal lymph node dissection	32 (74%)	24 (56%)	0.72
Use of catecholamines	4 (10%)	6 (14%)	0.43
Surgical procedure			
Pneumonectomy	0 (0%)	0 (0%)	-
Lobectomy	37 (86%)	33 (77%)	0.27
Segmentectomy or wedge resection	5 (12%)	9 (21%)	0.25
Lung cancer staging			
IA, IB	34 (79%)	30 (70%)	0.33
IIA, IIB	6 (14%)	7 (16%)	0.77
IIIA, IIIB	3 (7%)	6 (14%)	0.30
VC, % predicted	101 ± 13	105 ± 14	0.18
FEV_1, % predicted	82.8 ± 12	82.6 ± 12	0.63
DLco, % predicted	96.0 ± 22	94.2 ± 23	0.16
PaO_2, Torr	86.5 ± 9.5	85.3 ± 9.4	0.28
$PaCO_2$, Torr	38.6 ± 5.1	38.5 ± 3.5	0.86
BNP, pg/ml	53.0 (20.7–79.2)	44.0 (23.7–56.9)	0.39
COPD-GOLD stages			
I	23 (54%)	25 (58%)	0.67
II	18 (42%)	17 (40%)	0.83
III	2 (5%)	1 (2%)	0.56

[a]Values are shown as numbers (%), means ± SD or medians with an interquartile range.
ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BNP: B-type natriuretic peptide; DLco: diffusion capacity of the lung for carbon monoxide; FEV_1: forced expiratory ventilation in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease; $PaCO_2$: carbon dioxide blood partial pressure; PaO_2: arterial oxygen blood partial pressure; VATS: video-assisted thoracoscopic surgery; VC: vital capacity.

group, and the hANP group had significantly higher BNP levels before surgery than the control group because of the patient selection, as previously mentioned (Table 1).

Propensity score matching analysis

Of the 202 patients, 86 were extracted using propensity score matching to confirm the significant effects of hANP during the perioperative period. Their background characteristics were matched, as shown in Table 2.

Incidence of postoperative cardiopulmonary complications

Postoperative cardiopulmonary complications were identified in 53 (35%) control group patients and 7 (14%) hANP group patients; they are listed in Table 3. The incidence of postoperative cardiopulmonary complications was significantly lower in the hANP group ($P = 0.004$); nevertheless, there were more high-risk patients in the hANP group. The most common complication in both groups was arrhythmias, and the incidence of cardiovascular complications was significantly lower in the hANP group ($P = 0.037$). The incidence of respiratory complications was also significantly lower in the hANP group ($P = 0.044$). In the patients with propensity score matching analysis, the incidence of postoperative cardiopulmonary complications was also significantly lower in the hANP group ($P = 0.0004$, Table 4).

Operative mortality

The overall operative mortality was 1.0% (two patients). The causes of death were acute respiratory distress syndrome and acute myocardial infarction, both in the control group.

Haemodynamics

There were no significant differences between the groups in systolic blood pressure, diastolic blood pressure and heart rate during the perioperative period (Fig. 1). There were similar results in the analysis of the propensity score-matched groups.

Postoperative white blood cell counts and C-reactive protein levels

The hANP group had significantly lower WBC counts and CRP levels than the control group 3 and 7 days, as well as 1 month, after surgery (Fig. 2), even though the period of hANP infusion was only 3 days. There were similar results in the analysis of the propensity score-matched groups.

DISCUSSION

The present results indicate that low-dose hANP has a prophylactic effect against postoperative cardiopulmonary complications in COPD patients following pulmonary resection for lung cancer. We also performed propensity score matching analysis to reduce treatment selection bias. This analysis clarified the effects of hANP on postoperative cardiopulmonary complications. The present findings indicate that low-dose hANP administration is a valuable treatment option to prevent postoperative cardiopulmonary complications in untreated COPD patients undergoing thoracic surgery.

It has been reported that the sympathetic nervous system, as well as renin-angiotensin activity, is activated in COPD patients [14]. It is well known that enhanced sympathetic nervous system activity is associated with the pathophysiology of cardiovascular events. Several studies have demonstrated an increased risk of cardiovascular complications in COPD patients after lung cancer surgery compared with the general population [4, 5]. It is known that hANP has cardioprotective effects, including inhibition of sympathetic nervous system activity and the renin-angiotensin-aldosterone system [15, 16]. Sezai *et al.* [15] reported that low-dose hANP infusion (0.02 μg/kg/min) did not significantly change haemodynamics, but reduced renin activity

Table 3: Postoperative cardiopulmonary complications in COPD patients after lung cancer surgery

	hANP group ($n = 51$)	Control group ($n = 151$)	*P*-value
All cardiopulmonary complications	7 (14%)	53 (35%)	0.004*
Cardiovascular complications	6 (12%)	39 (26%)	0.037*
Atrial fibrillation	5	34	
Paroxysmal supraventricular tachycardia	1	2	
Acute myocardial infarction	0	3	
Respiratory complications	1 (2%)	17 (11%)	0.044*
Pneumonia	1	13	
Acute respiratory distress syndrome	0	4	

*Significant ($P < 0.05$).

Table 4: Postoperative cardiopulmonary complications in the patients with propensity score matching analysis

	hANP group ($n = 43$)	Control group ($n = 43$)	*P*-value
All cardiopulmonary complications	4 (9%)	18 (42%)	0.0004*
Cardiovascular complications	3 (7%)	11 (26%)	0.0193*
Atrial fibrillation	3	7	
Paroxysmal supraventricular tachycardia	0	1	
Acute myocardial infarction	0	3	
Respiratory complications	1 (2%)	8 (19%)	0.0133*
Pneumonia	1	6	
Acute respiratory distress syndrome	0	2	

*Significant ($P < 0.05$).

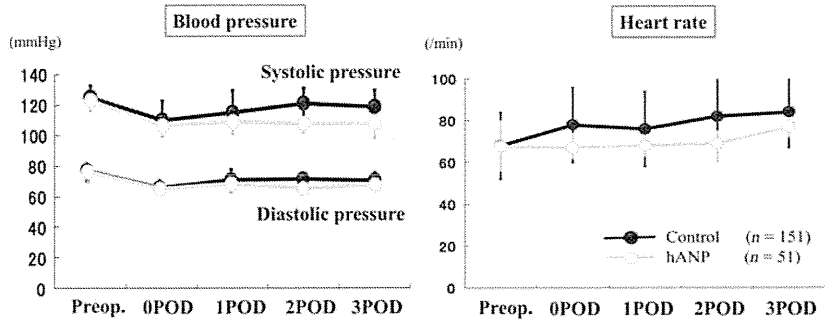

Figure 1: Changes in perioperative systolic blood pressure, diastolic blood pressure and heart rate. Each point with bars shows the mean ± SD.

and angiotensin- and aldosterone levels, which prevented postoperative cardiovascular complications after coronary artery bypass grafting [16].

Left ventricular (LV) diastolic dysfunction has often been recognized in COPD patients [17]. LV diastolic dysfunction has also been associated with an increased risk of cardiovascular events [18]. We previously reported that patients with LV diastolic dysfunction before lung cancer surgery have an increased risk of postoperative atrial fibrillation [19]. It is known that hANP has beneficial effects on LV diastolic dysfunction [20]. Nakajima *et al.* [20] reported that atrial natriuretic peptide (ANP) infusion improved LV diastolic function in patients with mild to moderate heart failure. We previously reported that hANP had a prophylactic effect against postoperative atrial fibrillation in patients with elevated preoperative BNP levels [21]. These studies suggest that hANP attenuates sympathetic nervous system activity and impairs LV diastolic function during the perioperative period and exerts cardioprotective effects after surgery, which might lead to a prophylactic effect for COPD patients, preventing cardiovascular complications in the present study.

COPD is not simply a lung disease but a type of systemic inflammatory disease. Cigarette smoking has been shown to induce inflammatory changes in the lung that are characterized by the recruitment and activation of inflammatory cells, including alveolar macrophages and neutrophils [22]. Furthermore, recent reports show evidence that long-term smoking leads to systemic inflammation, possibly through spillover from the pulmonary inflammatory process. COPD patients have higher levels of systemic inflammatory markers, including CRP, fibrinogen, tumour necrosis factor-alpha and interleukin 6 [23]. Furthermore, recent reports suggest that the mechanism linking increased cardiovascular disease and COPD is potentially explained by systemic inflammation, including CRP [24]. ANP has recently been shown to have remarkable anti-inflammatory effects. Several studies have shown that ANP attenuates several pathways of inflammation *in vitro* and *in vivo*, suggesting its role in the regulation of pulmonary function in the setting of acute lung injury and pulmonary inflammation [8, 25]. Xing *et al.* [8] reported that ANP attenuated activation of inflammatory signalling by lipopolysaccharide and tumour necrosis factor-alpha in human pulmonary endothelial cells and protected against bacteria-induced lung injury and pulmonary endothelial barrier dysfunction. Mitaka *et al.* [25] reported that hANP infusion improved pulmonary gas exchange in patients with acute lung injury during mechanical ventilation. Furthermore, we previously reported that hANP had a prophylactic effect not only on cardiovascular but also on pulmonary complications in elderly patients [9]. These

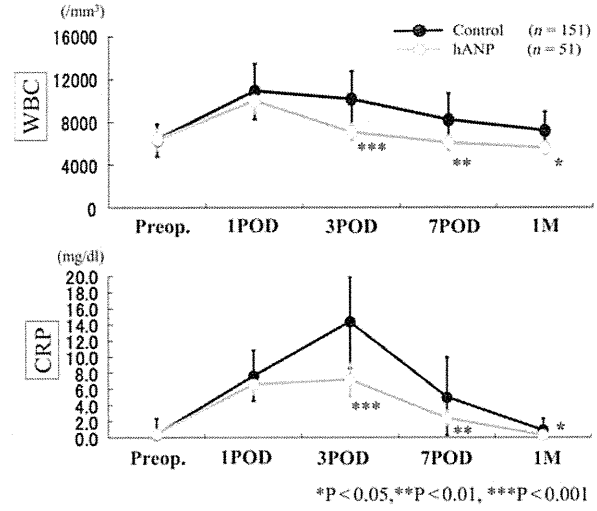

Figure 2: Changes in white blood cell counts and C-reactive protein levels in patients undergoing elective pulmonary resection for lung cancer who did and those who did not receive an infusion of hANP. Each point with bars shows the mean ± SD. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, POD: postoperative day; M: month; Preop: preoperative.

studies suggest that hANP attenuates systemic inflammatory changes, including pulmonary inflammation, and protects the function of pulmonary endothelial cells after surgery, which might lead to a prophylactic effect for COPD patients, preventing both cardiovascular and respiratory complications in the present study.

This study was a two-institution clinical study, which restricted our ability to generalize the results. In addition, the patients were not assigned to the groups randomly. Furthermore, the number of patients in the study cohort was relatively small. Thus, additional investigations with a larger number of patients from multiple institutions are necessary to allow generalization of the findings obtained here.

The present study is the first to show the prophylactic effects of low-dose hANP on postoperative cardiopulmonary complications in untreated COPD patients undergoing pulmonary resection for lung cancer. Additional studies are warranted to determine whether these effects can be observed in other patients and translated into improved clinical outcomes.

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Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

***Dr B. Passlick** (Freiburg, Germany)*: What are you planning for the future? Are you going for a randomized trial, or what is the objective?

***Dr Nojiri*:** We have already conducted randomized human ANP therapy, and probably next year, we will start the randomized study on lung cancer surgery.

***Dr Passlick*:** You mentioned in your abstract that you are able to also decrease respiratory complications. What is the mechanism? How can you explain that?

***Dr Nojiri*:** Pulmonary endothelial cells have a high expression of granylate cyclase A receptor, which is the specific receptor of ANP and BNP. ANP has recently been shown to have remarkable anti-inflammatory effects for pulmonary inflammation via the GCA receptor of the pulmonary endothelial cells. Several studies have shown that ANP attenuates activation of inflammatory signalling, such as NFkB and Rho signalling, by LPS or TNF-alpha in *in vitro* and *in vivo* models.

In human studies, Mitaka et al. reported in 1998 that human ANP infusion improved pulmonary gas exchange in patients with acute lung injury during mechanical ventilation.

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CASE REPORT

Yellow nail syndrome with thoracic empyema: report of a case

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Abstract We report a rare case of yellow nail syndrome (YNS) complicated by thoracic empyema. The patient was a 75-year-old man with yellow nails and a history of respiratory illnesses. Initially he presented with recurrent pleural effusion, which developed into empyema within 3 years. This case serves to reinforce that recurrent pleural effusions should be initiated in the early stage of YNS to prevent the development of empyema.

Keywords Yellow nail syndrome · Empyema · Decortication · Pleural effusion · Edema

Introduction

Yellow nail syndrome (YNS) is a rare disorder characterized by yellow nails, lymphedema, and chronic respiratory manifestations [1]. Although cases of recurrent pleural effusions associated with YNS have been reported [1–3], the development of thoracic empyema is extremely rare. We report a case of thoracic empyema in a patient with YNS.

Case report

A 75-year-old man was admitted to the Emergency Department of a municipal hospital with shortness of breath, high temperature, and coughing up of purulent sputum. During radiation therapy for prostate cancer at a university hospital 3 years earlier, a right-sided pleural effusion had been noted. He was referred to the municipal hospital to determine the cause of the pleural effusion; however, no definite diagnosis was made and the effusion diminished without any intervention. Another left pleural effusion was noted 3 months prior to the present admission. The pleural fluid cultures grew *Pseudomonas aeruginosa*, and treatment with antibiotics was effective. On admission, chest radiography and computed tomography (CT) showed a right pleural effusion, and the sputum and pleural fluid cultures again grew *P. aeruginosa*, but treatment with ceftazidime and gentamicin for 2 weeks was unsuccessful. The patient was referred to our hospital for the surgical treatment of empyema of unknown cause.

The patient reported that he drank about a can of beer every evening, but had never smoked. Pulmonary tuberculosis had been diagnosed at age 18, he had suffered benign prostatic hyperplasia at age 63, bronchiectasis had been diagnosed based on the clinical presentation at age 65, and he had undergone surgery for chronic sinusitis at age 68 years. At age 69, he became aware of the changes in his fingernails and toenails, and YNS was diagnosed at a local clinic.

On examination, the patient appeared chronically ill and under mild respiratory distress. Breath sounds were suppressed and wheezes were audible throughout the right lung field. He had moderate ankle edema and yellowish-brown nails with excessive side-to-side curvature (Fig. 1).

Chest radiography confirmed bilateral pleural effusion, and echocardiography revealed a small amount of pericardial effusion. Chest CT revealed bilateral pulmonary infiltrates and pleural effusions, multiple loculations in the right pleural space, and thickening of the parietal and

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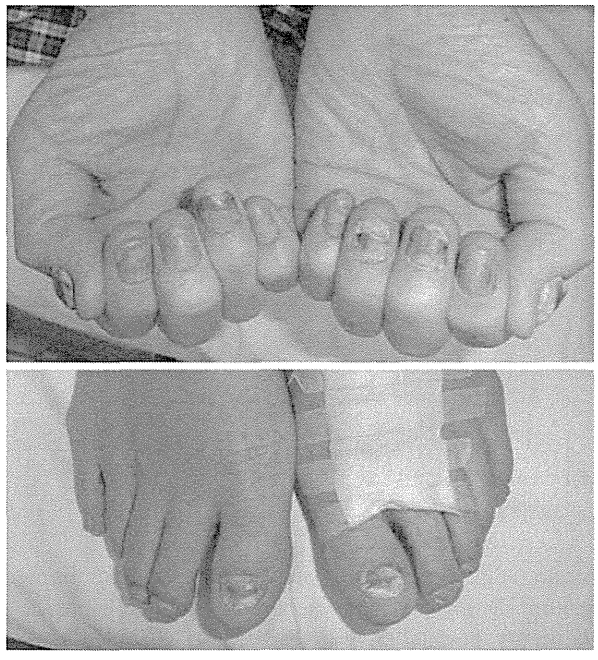

Fig. 1 Thickening and yellow discoloration of the patient's fingernails and toenails

visceral pleura, but the characteristic changes of bronchiectasis were not obvious (Fig. 2). ^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography revealed no FDG uptake, which suggested the absence of a malignant tumor. Bronchoscopy revealed inflammation of the airway mucosa, and endotracheal aspirates cultures grew *P. aeruginosa*.

A large-bore drainage tube was inserted into the right thoracic cavity, and the culture of the pus-like discharge grew *P. aeruginosa*. There was no air leakage. Thus we diagnosed fibrinopurulent or organizing thoracic empyema.

Red blood cells and albumin were transfused to treat the severe hypoalbuminemia (1.6 g/dl) and anemia (7.1 g/dl) resulting from chronic inflammation. After 2 weeks of thoracic cavity drainage and lavage, video-assisted thoracoscopic surgery was performed under local anesthesia. This revealed that the empyema had progressed to the organizing phase. We removed the fibrin deposits and multiple loculations that hindered effective chest drainage. The need for additional transfusions was avoided by giving a combination of parenteral and enteral nutrition. After another 1.5 months of thoracic cavity lavage, we performed thoracotomy with decortication and transposed a latissimus dorsi muscle flap. Through the therapeutic course in our hospital, we administered ceftazidime perioperatively only to prevent surgical-site infection. Despite temporal deterioration of the leg lymphedema after surgery, the patient made a slow but steady recovery, and was

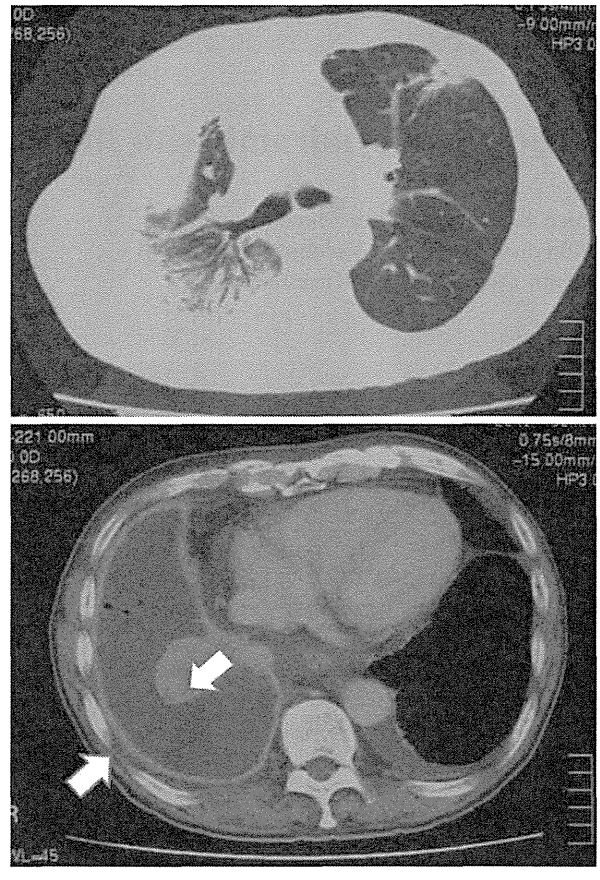

Fig. 2 Chest computed tomography scans showing bilateral pleural and pericardial effusion. The right pleural space was separated into loculations by the septum (*between the arrows*), and the parietal and visceral pleura were thickened

discharged on postoperative day 57. He is now only on a house diet and has not suffered a relapse of the infection (Fig. 3).

Discussion

Yellow nail syndrome is a rare disorder, first described in 1964 by Samman and White. Diagnosis is usually based on the classic triad of yellow nails, lymphedema, and chronic respiratory illness in the absence of other more likely explanations [1]. Approximately 150 cases of YNS, consisting of small case series or isolated case reports, have been documented [2]. The characteristic nail changes include thickening, transverse ridging, diminished growth, increased curvature, and deficient cuticles [4, 5]. The respiratory manifestations are diverse and include pleural effusion, bronchiectasis, rhinosinusitis, chronic cough, or recurrent lung infections [1]. Our patient presented with the

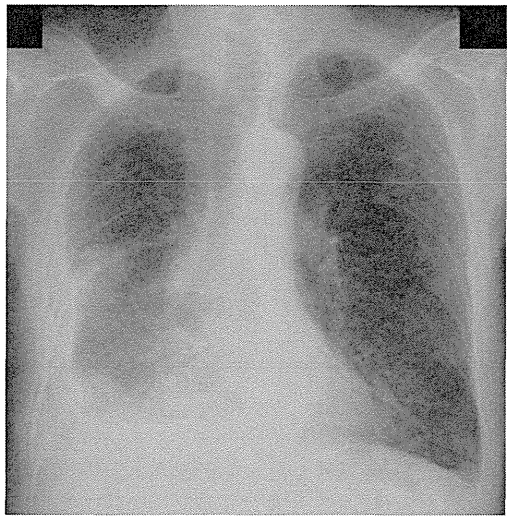

Fig. 3 Follow-up chest radiography showed no evidence of the reaccumulation of pleural fluid

characteristic yellow nails and recurrent respiratory infections.

The reason for the nail color and the pathophysiology of the syndrome remain unclear, but various anatomic or functional lymphatic drainage abnormalities have been proposed as the underlying cause [1]. Treatment of the nail disorder is unrewarding, although some patients seemed to associate improvement in their nails with better control of their respiratory symptoms, particularly recurrent infections [1]. Our patient had no pulmonary infections or lymphedema and his nails showed no improvement, even 12 months after surgery. Patients with a congenital deficiency of the lymphatic system often do not suffer persistent lymphedema until an episode such as trauma or infection increases the local capillary permeability, resulting in an increased load on the deficient lymphatic vessels [5]. In our patient, the temporal deterioration of lymphedema during the postoperative period was possibly caused by this mechanism.

Pleural effusion in YNS is also thought to occur secondary to dysfunction of the pleural lymphatics [3]. Pleural effusion, accompanied by repeated pulmonary infections, tends to persist in these patients and is treated with chemical pleurodesis, open pleural abrasion, pleuroperitoneal shunting, and pleurectomy [3]. The vacuum-assisted closure therapy system, which was recently reported to be beneficial for thoracic empyema, may be useful for the management of pleural effusion associated with YNS [6]. However, to the best of our knowledge only two cases of empyema occurring in association with YNS have been documented [5, 7]. One of these reports [5] suggested that empyema was caused by infection introduced during drainage of the recurrent effusion. It is probable that the empyema in our patient was caused by repeated episodes of pneumonia and pleuritis by *P. aeruginosa* because the same organism was cultured from the sputum and the pleural effusion fluid. Considering that the microorganisms in two previous reports were *Streptococcus pneumoniae* [5] and anaerobic species [7], the same mechanism as in the present case was possibly responsible for the development of empyema in these cases. The fact that all three patients needed invasive therapy, such as fenestration and decortications, indicates the limitation of conservative therapy against empyema with YNS, and the importance of managing pleural effusion early in patients with YNS.

In summary, we reported a rare case of thoracic empyema complicated by YNS to emphasize the importance of appropriate management for this syndrome. To control the accumulation of pleural effusion, YNS patients should take bronchopulmonary hygiene measures and seek treatment early for their respiratory infections. Furthermore, to prevent pleural effusion from developing into empyema, appropriate therapeutic intervention, starting with pleurodesis and stepping up to surgical procedures, should be initiated at an early stage of the syndrome.

Conflict of interest Toru Kimura and his co-authors have no conflict of interest.

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症 例

胸腔鏡補助下に摘出した肋骨発生線維性骨異形成の1例

楠本 英則，竹内 幸康，大瀬 尚子
桃實 徹，前田 元

要 旨

症例は28歳男性，検診胸部X線検査にて左第5肋骨の腫大を指摘され，当院を受診した．自覚症状はなく，既往歴・外傷歴も特になかった．胸部CT検査にて左第5肋骨腫瘍と診断し手術を施行した．手術は左腋窩小切開にて行い，病変の進展範囲を確認するために胸腔鏡を併用した．腫瘍は周囲組織へ浸潤傾向を示しておらず，腫瘍より約3 cmのmarginをとった位置で左第5肋骨を切除した．病理組織検査の結果は線維性骨異形成であった．胸腔鏡は病変部位および進展範囲の確認に有用であると考えられる．

索引用語：線維性骨異形成，肋骨，胸腔鏡手術
fibrous dysplasia, rib tumor, video-assisted thoracoscopic surgery

はじめに

線維性骨異形成は成因不明の非腫瘍性骨病変で，骨組織が化生骨を含む線維組織に置き換わる一種の形成異常と考えられている．今回，肋骨腫瘍の診断にて胸腔鏡補助下に第5肋骨を切除した1例を経験したので報告する．

症 例

症 例：28歳，男性．
主 訴：特になし．
家族歴：特になし．
既往歴：特になし．
現病歴：胸部X線検査にて胸壁腫瘍を指摘され当院紹介となった．
入院時現症：身長171 cm，体重72.6 kg，呼吸音は清明で身体所見に異常を認めなかった．
入院時血液検査所見：異常を認めなかった．
胸部X線所見(Fig. 1)：左第5肋骨の限局性肥厚を認めた．

独立行政法人国立病院機構刀根山病院 呼吸器外科
原稿受付 2011年6月27日
原稿採択 2011年8月17日

胸部CT所見(Fig. 2)：第5肋骨の中央部が6 cm長にわたり限局性に膨隆しており，同部位の骨皮質の菲薄化が見られた．腫瘤は骨皮質に覆われており，周囲

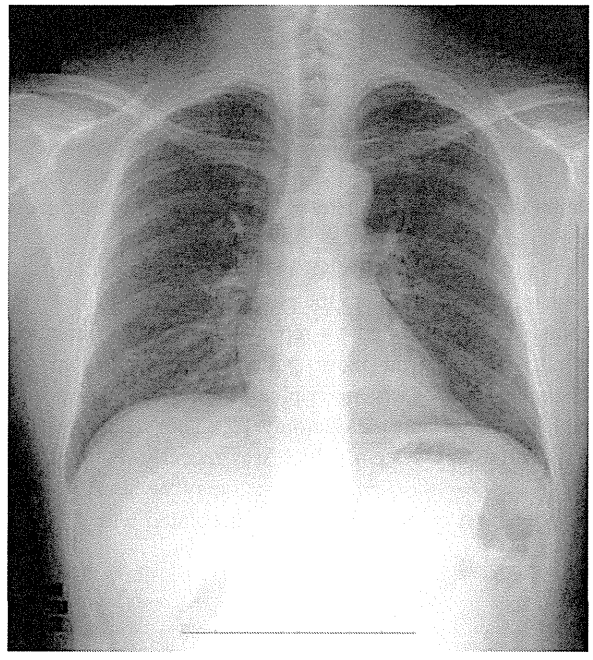

Fig. 1 Chest radiograph showing localized enlargement of the left fifth rib.

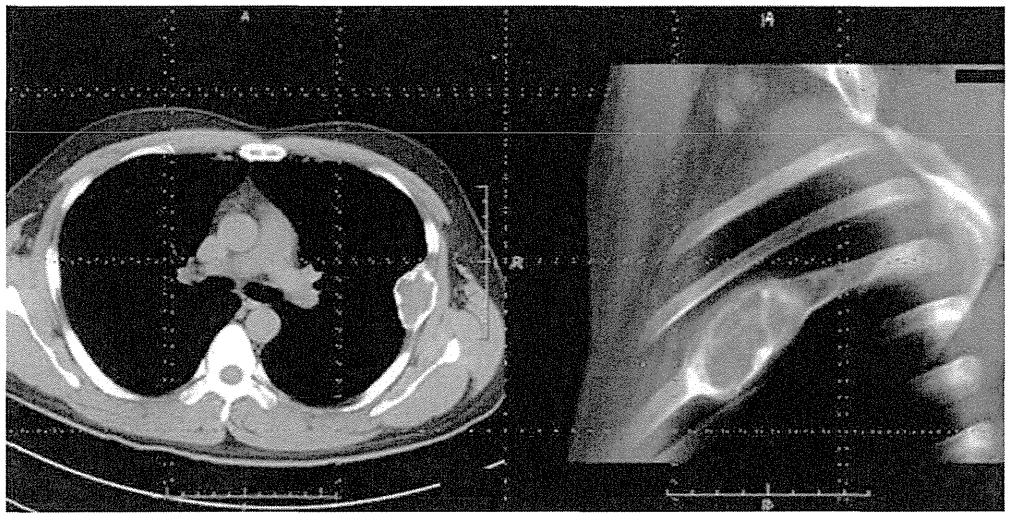

Fig. 2 Chest CT suggested a tumor of the left fifth rib, which was surrounded with a thin bone cortex.

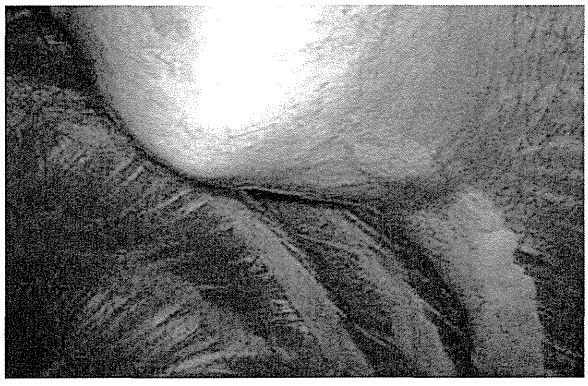

Fig. 3 Thoracoscopy revealed no tendency of the tumor to invade adjacent organs.

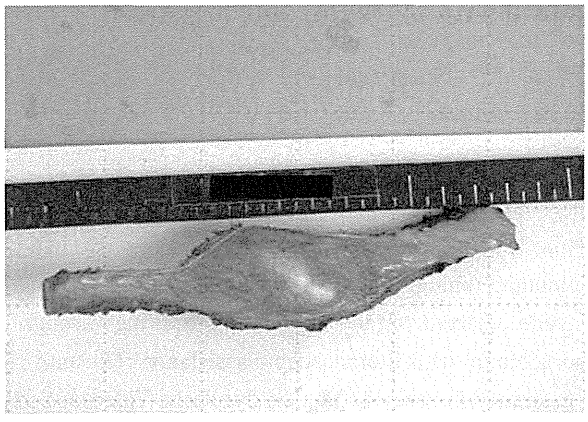

Fig. 4 Resected specimen of the left fifth rib. The tumor was 5.8 × 2.1 × 2.5 cm and showed a fusiform enlargement.

への浸潤の所見は認めなかった.

入院後経過：上記より左第5肋骨腫瘍（線維性骨異形成または巨細胞腫）の診断にて胸腔鏡補助下に左第5肋骨腫瘍切除術を施行した.

手術所見（Fig. 3）：右側臥位，左腋窩に縦に小切開をおき，第5肋骨を露出した．第7肋間中腋窩線にポートを留置し，胸腔内を観察した．腫瘍は第5肋骨に限局しており，肺との癒着なく周囲への浸潤所見を認めなかった．腫瘍より約3 cmのmarginをとった位置で肋骨剪刀にて肋骨を切断し腫瘍を摘出した.

切除標本肉眼所見（Fig. 4）：腫瘍は長径58 mmで最大幅は25 mmで，紡錘状に腫大していた．固定後で正常骨髄との境界は明瞭であった.

病理組織学的所見（Fig. 5）：線維芽細胞の増殖巣からなり，内部に地図状，鉤状の未熟な骨梁が島状に散見された．骨芽細胞による骨梁の縁取りはほとんど見られず，軟骨形成も明らかでなかった．線維芽細胞に核の異型や分裂像を認めず線維性骨異形成と診断された.

考　察

線維性骨異形成（以下，本症）は，成因不明の非腫瘍性骨病変で，骨組織が化生骨を含む線維組織に置き換わる一種の形成異常と考えられている．単骨性と多骨性に分類され，多骨性のもので皮膚色素沈着，性的早熟を伴うものはAlbright症候群と呼ばれる[1]．岡崎

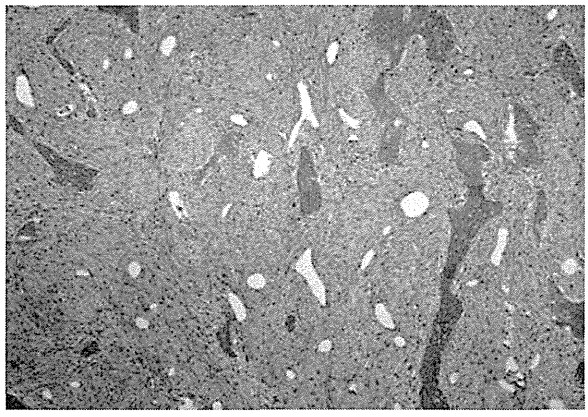

Fig. 5 Histologically, the tumor was composed of immature bone trabeculae with the proliferation of fibroblasts, and showed no malignant features of osteoblasts or fibroblasts.

らは，男女比は1.7：1で男性に多く，20～30歳代に好発すると報告した[2]．大腿骨，脛骨，肋骨の順に好発するとされ[3]，無症状のことが多いが，疼痛・腫脹・変形・病的骨折で発見されることもある．治療法は，手術のみが治療法となる．骨折の危険性が少なく，臨床症状の軽い症例では経過観察されることもあるが，単骨性の約0.5%，Albright症候群の約4%に悪性化が見られるとの報告がある[4]．単骨性の本症は無症状のことが多いが，外傷の既往がなく急速に増悪する持続的な痛みは悪性化の可能性があるとされる[5]．

本症の予後は単骨性の場合，切除されればほぼ無再発にて経過する．肋骨発生の場合は長管骨に比べ切除後の機能障害が少ないため，十分な距離をとって切除し，再発防止を優先することが大切である．本症例では，胸腔鏡を併用することで病変の進展範囲を確認し，腫瘍より十分距離をとった位置で肋骨を切除することができた．本症は術前診断や術中迅速診断が困難であり，悪性の骨腫瘍も念頭に置いた上で，十分な切除範囲を確保することが必要と考える．

結　　語

肋骨発生線維性骨異形成の1切除例を報告した．肋骨腫瘍切除に際し，胸腔鏡は病変部位および進展範囲の確認に有用と考えられた．

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A resected case of fibrous dysplasia of the rib with thoracoscopic assistance

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A 28-year-old man was admitted because of enlargement of the left fifth rib on a chest radiograph film. He had no symptoms and no past medical history nor traumatic injury. Computed tomography suggested a tumor of the left fifth rib. We observed that the tumor exhibited no tendency to invade adjacent organs by video monitoring through a thoracoscope. Resection was performed employing a small thoracotomy with thoracoscopic assistance. The fifth rib was resected with a margin of 3 cm to the tumor. Pathologic examination revealed fibrous dysplasia. Video-assisted thoracoscopic surgery is helpful to detect the location and the extent of tumor invasion.