during immunotherapy (data not shown). Lipford et al.[23] reported that among cells within enlarging lymph nodes are many DCs that express increased levels of costimulatory molecules and MHC. Interferon-γ is the final output produced either by the direct stimulation of lymphocytes or by the stimulation of lymphocytes secondary to activation of antigen-presenting cells such as DC. In vitro BCG-CWS induces IL-12 p40 production in peripheral blood culture. Interleukin-12 p40 is an inducible element of IL-12, and in humans may represent IFN-γ-inducing activity.[24]

According to a previous report,[18] BCG-CWS can induce IFN-γ when administered intracutaneously in a patient's upper arm. An elevated serum IFN-γ level is regarded as evidence of a systematic immune response. Interferon-γ is an important immune regulator that performs a wide spectrum of physiologic functions, such as activation of macrophages, NK cells, and CTL, regulation of antigen presentation in many cells, and generation of Type 1 helper T cells (Th1 cells).[25] Our data showed no significant difference in survival between the case-group patients with, and those without IFN-γ induction in the peripheral blood. In this study, we performed IFN-γ assay within 7 months after immunotherapy was started. Matsumoto et al.[24] reported that the levels of production of IFN-γ and IL-10 by lymphocytes were lower in patients with lung cancer than in healthy subjects. In our study, BCG-CWS was repeatedly injected into the skin of both shoulders, for more than 1 year in most patients. When patients receive long-term, repeated inoculations of BCG-CWS, the serum IFN-γ level may increase, especially in those with a good outcome. Our literature search found no report clearly stating an association between increased serum IFN-γ levels and survival benefit in patients receiving BCG-CWS immunotherapy. A recent study of NSCLC patients by Trojan et al.[26] suggested that peritumoral CD8+ T cells exhibit locally higher expression of IFN-γ mRNA; a finding indicative of sustained T-cell reactivity, compared with tumor-infiltrating T lymphocytes (TILs); however, they failed to demonstrate the influence of IFN-γ/CD8 mRNA ratio on overall survival in these patients.

We hypothesized that activation of the innate immune system with BCG-CWS after curative resection for lung cancer may have a survival benefit and conducted a case–control study. Although the difference was not significant, survival of the case-group patients was better than that of the control patients over a long-term follow-up period (Fig. 2). This trend was seen in the subgroups of pathological stage III or lymph node metastasis (Fig. 3C and D). However, there was no difference in survival between the subgroups of p-stage I or II (Fig. 3A and B). These results suggest that monotherapy using BCG-CWS may improve survival without major complications after curative surgery for lung cancer. Patients with advanced lung cancer, especially those with lymph node metastasis, seem to be good candidates for this innate immunotherapy. When patients have micrometastasis to distant lymph nodes, specific cancer antigens may be expressed by the cancer cells and recognized by mature myeloid DC activated with BCG-CWS. The survival benefit of BCG-CWS adjuvant therapy in this series was 17% at 10 years after surgery (Fig. 2A). Tanaka[27] reported a single-institute phase II trial of adjuvant chemotherapy with carboplatin/paclitaxel followed by tegafur and uracil (UFT) for completely resected node-positive (p-stage II-N1 or IIIA-N2) NSCLC. His interim analysis revealed favorable overall and recurrence-free survival of 73% and 49%, respectively, at 3 years, with minimal toxicity. These results suggest that chemotherapy followed by BCG-CWS immunotherapy should be prescribed in a postoperative adjuvant setting after NSCLC resection.

Regarding histological differences between the case and control groups, it was very difficult to completely match three factors at the time of control recruitment. Thus, we gave priority to pathological stage and year of birth. Histology was considered as much as possible but perfectly matched pairing was impossible. According to the survival analysis of BCG-CWS and historical control groups by Yasumoto et al.,[28] all types of lung cancer including squamous cell carcinoma, adenocarcinoma and anaplastic carcinoma were sensitive to treatment with BCG-CWS, and there was no significant difference in survival among those histological types. Their results suggest that the histological differences between case and control group are not of great consequence.

To achieve more effective control of cancer, two modalities should be used with BCG-CWS. The first is the coadministration of a peptide vaccine with BCG-CWS as the adjuvant. The Wilms' tumor gene, *WT1*, is overexpressed in leukemia and a variety of solid tumors, and the WT1 protein has been identified as a tumor-associated antigen.[29] Thus, WT1 products may provide the basis for the development of a new peptide-based anti-cancer immunotherapy. It was demonstrated that 3.0 mg of WT1 therapy can induce a generation of WT1-specific T lymphocytes without damaging normal tissues.[30] Nakajima et al.[31] demonstrated for the first time that a WT1 peptide vaccination combined with BCG-CWS effectively eradicated WT1-expressing tumor cells implanted in mice before vaccination; as a "therapeutic" model, not a "prophylactic" model. Vermorken et al.[32] reported that adjuvant active specific immunotherapy with an autologous tumor cell; namely, BCG (but not CWS) vaccine following surgical resection was more beneficial than resection alone against stage II and III colon cancer. The second modality is the stimulation of NK cells to lyse MHC-unrestricted cancer

cells. A high concentration of IL-10 in the tumor microenvironment may stimulate NK cells to lyse cancer cells, leading to increased availability of tumor-associated antigens and delivery of biologically active molecules, such as heat-shock proteins, needed for the activation of DCs and for effective priming of CTLs against tumor-associated antigens.[33]

We need good manufacturing practices to purify adjuvants such as BCG-CWS for translational research and to coadministrate with more personalized peptide vaccines as a future challenge. In conclusion, our results suggest that BCG-CWS immunotherapy following radical surgery for NSCLC improves overall survival without compromising quality of life.

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JOURNAL OF MEDICAL CASE REPORTS

Case report

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Malignant pleural mesothelioma with long-term tumor disappearance of a local relapse after surgery: a case report

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Abstract

Introduction: There have been few reports of spontaneous regression of malignant pleural mesothelioma, but the mechanism for this is unknown. We present a case report on a patient with malignant pleural mesothelioma showing apparent tumor disappearance in a local relapse after surgery.

Case presentation: A 73-year-old man presented with malignant pleural mesothelioma in the right thoracic cavity. A pleurectomy was performed, and as expected, the tumor locally relapsed with increasing chest pain. However, the symptoms suddenly improved while the tumor was apparently reduced, and spontaneous tumor regression was initially considered. The patient confessed that he had self-administered a mushroom extract with alternative parasympathetic nerve stimulation therapy thereafter. The complete disappearance of the tumor was clinically achieved during a 29-month follow-up with continuing self-treatment.

Conclusion: This is the first report describing a malignant pleural mesothelioma patient in Japan showing long-term complete disappearance of a local relapse after surgery. This event was a tumor regression possibly due to an immunological effect of combined complementary and alternative therapy.

Introduction

Although the standard therapy for malignant pleural mesothelioma (MPM) is still undetermined, the major therapeutic modality for this disease is surgery, radiation and chemotherapy. The majority of cases are at an advanced stage, thus several novel modalities to improve the overall survival time have been preliminarily explored. Immunotherapy, molecular-targeted therapy, and gene therapy are candidate therapies, but cases of long-term survival are exceptional.

In spite of the advanced-stage disease, complete or marked regression of MPM has been described [1–4]. These surprising events are mostly due to chemotherapy achieving complete remission [1], and only three reports have described spontaneous regression of this disease [2–4]. Recently, a patient with MPM experienced a complete tumor regression of a local relapse after cytoreduction surgery. It is possible that this unique favorable event was due to the effect of combined complementary and alternative self-therapy.

Case presentation

A 73-year-old man with a 75-pack-year history of cigarette smoking and asbestos exposure between the ages of 30 and 40 years had been admitted to undergo an extrapleural pneumonectomy due to MPM in the right pleural cavity. However, only a cytoreduction pleurectomy was performed on 30 September 2003 (Figure 1A), because of the aggressiveness of the local tumor. The lesion remained mainly in the mediastino-hilar region adjacent to the carina, esophagus, and the right main bronchus. Histologically, the tumor was epithelioid type (Figure 1B) with T4N0, stage IV (IMIG staging). Then, postoperative intrathoracic chemothermotherapy using carboplatin (CBDCA, 450mg intrapleurally, one course) was administered, followed by systemic chemotherapy using gemcitabine (GEM, 0.8mg/m^2, biweekly, 6 courses). Chest computed tomography (CT) in December 2003 showed that the effect of these postoperative therapies on the residual tumor was stable disease (SD).

In May 2004, the patient felt increasing chest pain with poor general condition. Chest CT showed local relapse broadly in the right pleural cavity causing airway narrowing (Figure 2A). However, he refused further chemoradiation therapy, and in June 2004, without consulting

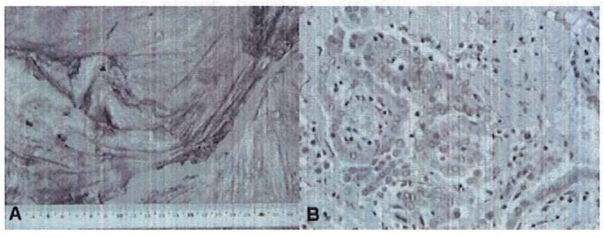

Figure 1
Macroscopic (A) and microscopic (B) findings of the surgically resected malignant pleural mesothelioma. Multiple nodules of malignant pleural mesothelioma were macroscopically scattered throughout the resected parietal pleura (A). Hematoxylin-eosin-stained light micrograph of the resected pleural tumor. The lesion was histologically diagnosed as epithelioid-type malignant pleural mesothelioma (B).

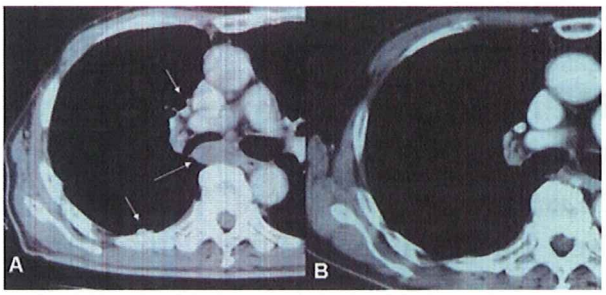

Figure 2
Local relapse before treatment (A) and tumor disappearance after treatment (B) on chest computed tomography. Chest computed tomography scan (A) before the combined therapy showing local relapse of malignant pleural mesothelioma in the right pleural cavity, especially with tumor mass formation in the mediastino-hilar region causing airway narrowing. White arrows show relapsed lesions in the right pleural cavity. After the combined therapy, chest computed tomography scan (B) shows complete tumor disappearance in the right pleural cavity.

with the physicians, he orally self-administered a mushroom extract containing Agaricus blazei Murill Kyowa (ABMK) [5], in addition to alternative parasympathetic nerve stimulation therapy in another hospital. This is a modified acupuncture modality providing possible immune-modulation [6]. After experiencing high fever for about 2 weeks, his general condition distinctly improved. Four months after these therapies, the relapsed bulky tumor in the pleural cavity had significantly decreased, and finally completely disappeared on chest CT (Figure 2B). Then, the patient continued this self-treatment with neither symptoms nor radiological evidence of tumor relapse in May 2007. Tumor disappearance was completely achieved during a 29-month follow-up.

Unfortunately, local relapse was detected on chest CT in August 2007. In November 2008, although the relapsed tumor was again growing slowly, the patient was alive while continuing this self-treatment.

Discussion

The median survival times for patients with an unresectable or postsurgical recurrent MPM are usually reported to be in the 6- to 12-month range with the best supportive care, and even now, most chemotherapeutic regimens have shown no or only a minor benefit to the survival rate. In this patient, although an extrapleural pneumonectomy was initially selected as the first step, only a cytoreduction pleurectomy was performed. Therefore, postoperative treatment including intrathoracic chemothermotherapy

and systemic chemotherapy was positively administered yielding SD, but unfortunately, a local re-growth of the tumor occurred later. Surprisingly, considering the usually poor prognosis of this disease, the present clinical course after a local relapse seems unique. It is extremely interesting to elucidate the mechanism of regression of the tumor.

Initially, the disappearance of the tumor was viewed as a result of the delayed effect of postoperative chemotherapy; however, by reviewing the clinical course and condition of the patient, this judgment was found to be negative. In addition, since the patient had taken non-steroidal anti-inflammatory drugs (NSAIDs) continuously after undergoing a pleurectomy, it also seemed that this medication had had little effect on the observed tumor regression. Next, a so-called "spontaneous regression" of the tumor was considered, because the patient did not reveal that he had received the "complementary or alternative combined therapy". Spontaneous regression of MPM has been described in only three reports [2–4]. A clinical summary of these reported cases is shown in Table 1. According to these reports, spontaneous regression of MPM may be strongly associated with lymphocyte-mediated immunity. Robinson *et al.* [2] emphasized an association between MPM regression and some immunological mechanism based on the histological observation of massive lymphoid infiltration within the tumor tissue. Pilling *et al.* [3] also reported similar histological findings. In our patient, however, such histological evidence was not seen in the surgically resected tissue.

Thirdly, after having revealed this "hidden combined therapy", tumor disappearance could be rather considered as a "therapeutic effect" of achieving complete remission. ABMK, a mushroom extract, is considered a health food in many countries after it was reported to be a potential source of anti-tumor, anti-metastatic, cytotoxic and immunoactive compounds [5, 7]. Experimentally, Kimura *et al.* [7] showed that some substances isolated from ABMK inhibited tumor growth through the mechanism of both anti-angiogenic and immune-modulatory activity. Ahn *et al.* [5] reported that natural killer cell activity was clinically elevated by ABMK-treated gynecological cancer patients. Another therapy, parasympathetic nerve stimulation therapy with a minor modification using a laser machine, is widely performed as alternative therapy for patients suffering from cancer as well as various other types of disease in Japan [6]. In particular, for cancer-bearing patients, it was said that acupuncture therapy could provide a beneficial effect in anti-cancer treatment by enhancing the cellular immune function [8]; however, so far, there has been no report describing the clinically complete remission of malignancy by these therapies.

Alternative, but more scientific, immunotherapy has been clinically explored to treat MPM [9]. One is specific immunotherapy which targets particular antigens in MPM tissue, and the other is a non-specific, but anti-tumor immunotherapy using such cytokines as interleukin 2 (IL-2), tumor necrosis factor (TNF), and interferon (INF) [9]. In fact, complete remission of MPM was experienced by INF administration through intra-pleural administration [10].

In our patient, considering that the timing of the improvements in his general condition after a high fever and tumor disappearance accorded with the influence of this "complementary or alternative treatment", it is likely that this successful clinical outcome resulted in complete remission. However, it is unknown whether the AGMK or parasympathetic nerve stimulation or both combined brought about the most favorable effect, and importantly, there are no scientific grounds to confirm the direct effect of this treatment. Several immunological blood parameters such as serum IL-2, INF-alpha, INF-gamma, and

Table 1. Reported cases of spontaneous regression of malignant pleural mesothelioma

Reporter Country	Year	Gender	Age	Histology	Previous therapy	Patient Time to regression Period of regression	Outcome	Mechanism
Robinson et al. [2] Australia*	2001	Female	54	Mixed (with lymphoid infiltration)	No	3 months Unknown	Died	Immunological reaction?
Pilling et al. [3] UK**	2007	Male	58	Epithelioid (with inflammatory response)	Surgery	Unknown 7 years	Survival without relapse	Host response
Allen RKA [4] Australia**	2007	Female	61	Epithelioid (poorly differentiated)	No	6 months 5 years	Survival without relapse	Immunological reaction?
The present case Japan**	2009	Male	73	Epithelioid	Surgery Chemotherapy	4 months 29 months	Survival with re-relapse	Complementary and alternative therapy?

*Case of spontaneous marked regression
**Cases of spontaneous complete regression

CD4/CD8 ratio were examined after the tumor disappearance, but all were within the normal range (data not shown).

In summary, this report presents a patient with MPM with a clinical tumor disappearance after a local relapse during a 29-month follow-up period. The mechanism of this tumor disappearance could not be sufficiently explained. Importantly, the mechanism of spontaneous regression of this disease in previous reports [2–4] is considered to be strongly associated with some immunological reaction, and the good effect of such complementary or alternative treatment modalities [5–8] is also caused by a similar immune response. Considering these data together, some immunological reactions of the host to the tumor are thus suggested to be responsible in this patient.

Conclusion

This is the first report describing a MPM patient in Japan showing long-term complete disappearance of a local relapse after surgery. The mechanism of this surprising tumor disappearance cannot be categorically explained. However, the clinical course suggests that some immunological reactions of the host to the tumor may be responsible.

Abbreviations

ABMK, Agaricus blazei Murill Kyowa; CBDCA, carboplatin; CT, computed tomography; GEM, gemcitabine; MPM, malignant pleural mesothelioma; IL-2, interleukin-2; IMIG, International Mesothelioma Interest Group; INF-alpha, interferon-alpha; INF-gamma, interferon-gamma; SD, stable disease; TNF, tumor necrosis factor.

Consent

Written consent was obtained from the patient for publication of the case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of the journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MH conceived the study concept and design, was involved with patient care and drafted the manuscript and literature review. KO, JO, JM: conceived the study concept and design, were involved with patient care and drafting the manuscript. KK: was involved with formation of the study concept and design and drafting the manuscript, FI: was involved with formation of the study concept and design, patient care and drafting of the manuscript and literature review. All authors have read and approved the final version of the manuscript.

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Pulmonary Resection in Patients Aged 80 Years or Over with Clinical Stage I Non-small Cell Lung Cancer

Prognostic Factors for Overall Survival and Risk Factors for Postoperative Complications

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Introduction: This retrospective study was designed to identify the predictors of long-term survival and the risk factors for complications after surgery in patients aged 80 years or older with clinical (c)-stage I non-small cell lung cancer.

Methods: The Japanese Joint Committee of Lung Cancer Registry collated the clinicopathological profiles and outcomes of 13,344 patients who underwent pulmonary resection for primary lung cancer in 1999. The data of 367 patients aged 80 years or older with c-stage I non-small cell lung cancer were analyzed for prognostic factors and risk factors for postoperative complications.

Results: The median age was 82 years (range, 80–90 years). Of the total patient number, 102 (27.8%) had some form of comorbidity diagnosed preoperatively. Thirty-one (8.4%) patients presented with postoperative complications, and the operative mortality was 1.4%. The 5-year survival rates were 55.7% for c-stage I patients, 62.0% for c-stage IA, and 47.2% for c-stage IB . Advanced pathologic stage and comorbidity were significant independent predictors of shortened survival ($p < 0.0001$ and $p = 0.032$, respectively). Comorbidity and mediastinal lymph node dissection were identified as factors that increased the risk of postoperative complications ($p < 0.0001$ and $p = 0.036$, respectively). Survival rates were independent of the extent of pulmonary resection (lobectomy or limited resection).

Conclusions: Octogenarian patients with c-stage I lung cancer in this study had a satisfactory long-term outcome and low-mortality rate. Comorbidity is a factor associated with both prognosis and operative risks. A selection of the patients who would be curable without mediastinal lymph node dissection after an accurate preoperative staging is beneficial to decrease the postoperative complications because this procedure is a risk factor.

Key Words: Clinical stage I lung cancer, Surgery, Octogenarian, Prognostic factor, Risk factor for postoperative complication, Limited resection.

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The average age of the general population is increasing in many countries including Japan.[1] According to the Japanese national statistics on population, the proportion of people older than 80 years will swell from 5.2% in 2006 to 9.6% in 2020.[2] Lung cancer is the leading cause of cancer-related deaths in many countries, and patients older than 80 years account for 14% of all lung cancers.[3,4] Thus, the number of elderly lung cancer patients is increasing rapidly worldwide.

The current gold standard treatment of early-stage lung cancer is the resection of the primary tumor plus the lymph nodes, whether they are involved or not.[5] Pulmonary resection is feasible and safe in octogenarians, given the appropriate selection of surgical candidates,[6–10] and evidence-based guidelines recommend that lung cancer patients should not be denied resection on the grounds of age alone.[11] However, elderly patients who undergo pulmonary resection have a higher incidence of morbidity and mortality than that of younger patients because of the increased incidence of adverse medical conditions and reduced cardiopulmonary function with aging.[12] In addition, the long-term benefit of surgery in elderly patients remains unclear because aging itself is an independent significant predictor of poor survival.[13,14]

Elderly patients are generally diagnosed with early-stage lung cancer compared with younger patients.[15] Although lobectomy is usually recommended for early lung

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cancer, limited surgery and other less invasive nonsurgical alternatives could be indicated if the patient has an increased risk of complications. Decisions regarding the treatment strategy must, therefore, carefully balance the risks of postsurgical morbidity and mortality with those affecting cancer recurrence and long-term survival.

The Japanese Joint Committee of Lung Cancer Registry conducted retrospective studies on cancer patients in 1989, 1994, and 1999 after a 5-year follow-up.[16,17] National data were collected for 13,010 lung cancers that were resected surgically in 1999. This study focused on patients aged 80 years and older with clinical (c)-stage I lung cancer to elucidate predictors of long-term survival and risk factors for postoperative complications.

PATIENTS AND METHODS

Registry

The Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on prognosis and clinicopathological profiles of patients with primary lung cancer surgically treated in 1999 in Japan. The committee received the registries of 13,334 patients from 387 teaching hospitals across Japan. The questionnaire comprised 32 items including gender, age, c-T, c-N, c-M, c-stage, preoperative treatment, surgical procedure (pneumonectomy, lobectomy, segmentectomy, or wedge resection), extent of lymph node dissection (ND0-1 or ND2: ND0, without lymph node dissection or lymph node sampling; ND1, intrapulmonary and hilar lymph node dissection; ND2, ND1 plus mediastinal lymph node dissection), curability, residual tumor, diameter of surgical tumor specimen, histology, pathologic (p)-stage, comorbidity, preoperative Eastern Cooperative Oncology Group performance status, postoperative complications, survival time, and cause of death. For the tumor, node, metastasis staging, chest radiograph, computed tomography (CT) of the chest, CT or ultrasound of the upper abdomen, whole-brain CT or magnetic resonance imaging, and bone scintigraphy were performed.

Patients

The study focused on patients with c-stage-I non-small cell lung cancer (NSCLC) in octogenarians. Of the 13,334 registered patients, 602 (4.5%) were aged 80 years or older. Clinical-stage-I patients accounted for 77.6% (467 patients) of this age group, nine patients (1.5%) with c-stage IIA, 55 (9.1%) with IIB, 46 (7.6%) with IIIA, 12 (2.0%) with IIIB, and six (1.0%) with c-stage IV (c-stage was not described in seven patients). One hundred patients were excluded because of previous treatment for lung cancer, incomplete resection, small cell carcinoma histology, low-grade malignant histology, or insufficient information on the factors of interest. The remaining 367 patients were enrolled in the study and followed for at least 5 years after surgery.

Comorbidities and Postoperative Complications

Comorbidities and postoperative complications were diagnosed and recorded during daily clinical practice by laboratory, radiologic, and physiological examinations. The questionnaires regarding comorbidity comprised 11 items: active smoking history within 1 month before surgery, obesity (body mass index, $\geq$30 kg/m^2), cerebrovascular or neurologic diseases, chronic obstructive pulmonary disease (forced expiratory volume in 1 second $\leq$40%), interstitial pneumonitis (apparent interstitial shadow detected by chest CT), ischemic heart disease (positive stress test), renal dysfunction (serum creatinine $\geq$2.0 mg/dl), liver cirrhosis (Child-Turcotte class B or worse), diabetes mellitus (HbA1C $\geq$8.0%), anemia (Hb $\leq$8.0 g/dl), and autoimmune disease. The postoperative complications were as follows: wound infection (accompanying wound failure), postoperative hemorrhage (500 mL/h or more), prolonged air leakage (2 weeks or longer), chylothorax (1500 mL/d or more), bronchopleural fistula, bronchovascular fistula, pulmonary embolism, empyema, pneumonia (presenting abnormal shadow by chest radiograph), respiratory failure (needed mechanical ventilation for 3 days or longer), myocardial infarction, and cerebral infarction.

Statistical Analysis

The survival time was measured from the date of surgery to the date of the most recent follow-up examination. Survival was calculated by the Kaplan-Meier method, and differences in survival were assessed by log-rank analysis. A multivariate analysis for prognostic factors was performed using the Cox proportional hazard regression model. A logistic regression model of the multivariate analysis results was used to identify the risk factors for postoperative complications. The p values less than 0.05 were considered statistically significant. Data are presented as mean $\pm$ standard deviation. Operative mortality included all patients who died within the first 30 days after surgery or during the same hospitalization.

RESULTS

Patient Characteristics

Table 1 summarizes the patient characteristics. The mean age was 82.3 years (median, 82 years; range, 80–90 years). The tumor histology was as follows: adenocarcinoma in 245 patients (66.8%), squamous cell carcinoma in 100 (27.2%), large cell carcinoma in 14 (3.8%), adenosquamous carcinoma in seven (1.9%), and one pleomorphic or sarcomatoid carcinoma. A total of 245 lobectomies and 122 limited resections were performed. Limited resections included 80 wedge resections and 42 segmentectomies. Concerning the c-T stage, limited resections were performed in 94 (43.9%) of 214 patients with cT1 diseases and 28 (18.3%) of 153 patients with cT2 disease. Pneumonectomies were not performed in this cohort. A systematic mediastinal lymph node dissection (ND2) was performed in 127 patients only. According to the c-T stage, ND2 was performed in 69 (32.2%) of the 214 patients with cT1 diseases and 58 (37.9%) of the 153 patients with cT2 disease. After pathologic diagnosis of the surgical specimens, 300 patients remained as stage I, whereas 67 patients were diagnosed with a more advanced disease including 44 stage II patients and 23 stage III patients. There were 53 pathologic node-positive patients (14.4%). The mean tumor diameter was 30.6 $\pm$ 14.9 mm, with 113 tumors (30.8%) smaller than 20 mm and 21 tumors (5.7%) larger than

TABLE 1. Characteristics and Overall 5-yr Survival Rates According to Potential Prognostic Factors of Clinical Stage I Patients (n = 367)

Variable	n	%	5-yr Survival Rate (%)	p
Age, median (range)	82 (80–90)		56.1	
Gender				
Male	232	63.2	47.9	0.0006
Female	135	36.8	68.8	
Performance status				
0 or 1	346	94.3	56.3	0.0563
2 or 3	21	5.7	37.1	
Smoking status				
Current smoker	40	10.9	30.2	<0.0001
Non-smoker or Ex-smoker	327	89.1	59.2	
Histology				
Adenocarcinoma	245	66.8	62.3	<0.0001
Squamous cell carcinoma	100	27.2	48.8	Adenocarcinoma vs. nonadenocarcinoma
Others	22	6.0	11.9	
Clinical T				
Clinical T1	214	58.3	62.4	0.0287
Clinical T2	153	41.7	47.2	
Comorbidity				
Yes	102	27.8	42.5	0.0007
No	265	72.2	61.0	
Operative procedure				
Lobectomy	245	66.8	53.8	0.9499
Limited resection	122	33.2	59.8	
Nodal dissection				
ND0-1	240	65.4	56.8	0.7616
ND2	127	34.6	53.7	
Pathological stage				
p-stage I	300	81.7	60.9	<0.0001
p-stage II or advanced	67	18.3	30.8	

ND, lymph node dissection; ND0, without lymph node dissection or lymph node sampling; ND1, intrapulmonary and hilar lymph node dissection; ND2, ND1 plus mediastinal lymph node dissection.

TABLE 2. Details of Preoperative Comorbidity

Type of Comorbidity	No. of Patients	%
Smoking	40	10.9
Obesity	1	0.3
Cerebro-neural diseases	17	4.6
Chronic obstructive pulmonary disease	13	3.5
Interstitial pneumonitis	5	1.4
Ischemic heart disease	22	6.0
Renal disease	3	0.8
Liver cirrhosis	0	0.0
Diabetes mellitus	12	3.3
Anemia	0	0.0
Autoimmune diseases	1	0.3
Total	102	27.8

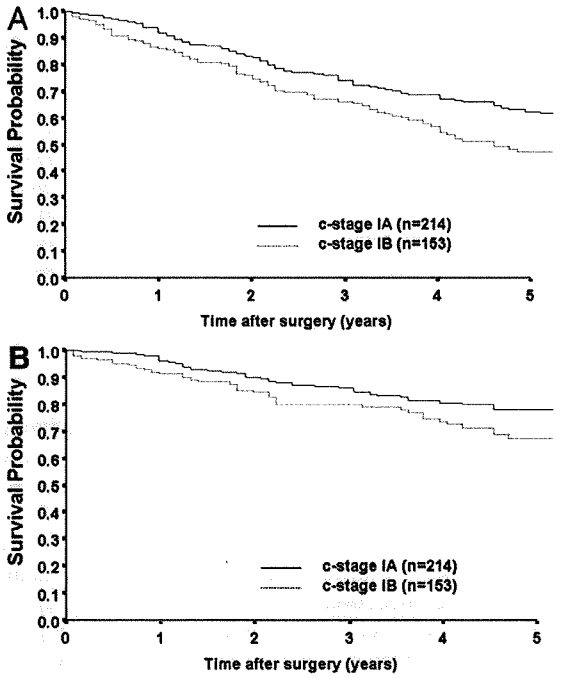

FIGURE 1. *A*, Postoperative overall survival curves according to the c-stage show a significant difference between c-stage IA and c-stage IB (p = 0.0287). *B*, Postoperative cause-specific survival curves according to the c-stage show a significant difference between c-stage IA and c-stage IB patients (p = 0.0440).

50 mm in diameter. Twenty-one patients (5.7%) had poor Eastern Cooperative Oncology Group performance status, and 102 patients (27.8%) were diagnosed with some type of comorbidity (summarized in Table 2) before surgery. Eighteen patients had two comorbidities and three patients had three comorbidities. The most common comorbidity was active smoking status within 1 month of surgery. Twenty-two patients (6.0%) had comorbid ischemic heart disease.

Analysis of Prognostic Factors

The 1-, 3-, and 5-year overall survival rates after surgery for octogenarian patients were 89.1%, 70.6%, and 55.7%, respectively, in c-stage I NSCLC cases, 91.6%, 73.8%, and 62.0%, respectively, for c-stage IA, and 85.7%, 66.1%, and 47.2%, respectively, for c-stage IB (Figure 1*A*). Because 53 patients (15.0%) were lost to follow-up, they were censored at the date of last contact with the institution. One hundred forty-six patients died of causes listed in Table 3. Five operative mortalities occurred within 30 days of surgery, and 71 deaths from cancer were considered lung cancer-related. No patients in this cohort died during the same hospitalization later than 30 days after surgery, and 52 patients died of other causes during the 5-year follow-up period. The calculated cause-specific 5-year survival rate

TABLE 3. Summary of Causes of Death During 5-yr Follow-up

Cause of Death	No. of Patients	%	Percentage of all Deaths
Surgical mortality	5	1.4	3.4
Lung cancer-related death	71	19.3	48.6
Other cancer-related death	8	2.2	5.5
Died of nonmalignant diseases	44	12.0	30.1
Unknown	18	4.9	12.3
Total	146	39.8	100

after surgery was 73.4%, 77.9%, and 66.9% for c-stage I, stage IA, and stage IB patients, respectively (Figure 1*B*).

A univariate analysis was used to evaluate the prognostic impact of nine clinicopathological factors listed in Table 1. Female gender, non-smoker or ex-smoker, adenocarcinoma histology, c-T1, absence of comorbidity, and p-stage I were significant prognostic factors for greater overall survival. In addition, a good performance status (0 or 1) was marginally significant. Neither the surgical procedure (lobectomy or limited surgery) nor the extent of nodal dissection (ND0-1 or ND2) was significantly associated with survival. Adenocarcinoma was associated with a significantly better prognosis than squamous cell carcinoma or other carcinoma. A multivariate analysis showed that p-stage I and absence of comorbidity were independent significant beneficial factors for overall survival, whereas female gender, adenocarcinoma histology, and better performance status were marginally significant (Table 4).

Risk Factors for Postoperative Complications

A total of 31 patients (8.4%) presented with postoperative complications (Table 5). Two complications occurred in five patients. The most common complications in order of frequency were pneumonia followed by prolonged air leakage (>2 weeks). A multivariate analysis identified mediastinal lymph node dissection (ND2) and comorbidity as significant factors associated with increased risk of postoperative complications (Table 6). Interestingly, performance status, which is a well-recognized risk factor, was not significantly associated with postoperative complications. The reason for this could be that there was a very few percentage of the patients with a poor performance status.

TABLE 5. Details of Major Postoperative Complications

Type of Complication	No. of Patients	%
Pneumonia	17	4.6
Prolonged air leakage	7	1.9
Cerebral infarction	3	0.8
Empyema	2	0.5
Wound infection	1	0.3
Bronchopleural fistula	1	0.3
Pulmonary embolism	1	0.3
Respiratory failure	1	0.3
Myocardial infarction	1	0.3
Other	2	0.5
Total	31	8.4

Five patients (1.4%) died within 30 days of surgery, and each had undergone a lobectomy. Table 7 summarizes the clinical courses of these patients: four had (a) comorbid disease(s) with pneumonia in three patients, cerebral infarction in two, and myocardial infarction and pulmonary embolism in one patient. Thus, the operative mortality rate was 2.0% (five of 245) after lobectomy and zero after limited resection.

DISCUSSION

Surgery offers the highest probability of cure in all patients with early-stage lung cancer. However, surgeons often hesitate to recommend surgery for elderly patients because of the higher perioperative risks and the uncertainty of long-term benefit. As Japanese citizens who are 80 years old are expected to live for an additional 8.2 years for men and 11.1 years for women,[2] a radical treatment should be considered. More information regarding the short-term and long-term postoperative outcomes would help surgeons to select a subgroup of elderly patients suitable for a pulmonary resection. This study analyzed 367 patients aged from 80 to 90 years with c-stage I NSCLC. These patients accounted for 2.8% of all lung cancers in the registry.

The long-term results in this study were satisfactory. The 5-year survival rate was superior to those reported recently in a large cohort of octogenarians: 48% for p-stage IA and 39% for p-stage IB,[10] although single institutional studies with smaller numbers of patients have presented

TABLE 4. Multivariate Analysis of Survival in Clinical Stage I Cases: Cox Proportional Hazard Model

Variable	Reference	HR	95% CI	*p*
Gender (female)	Male	0.691	0.466–1.027	0.067
Performance status (2 or 3)	0 or 1	1.829	0.977–3.423	0.059
Histology (non-adenocarcinoma)	Adenocarcinoma	1.390	0.966–2.000	0.076
Clinical T (cT2)	cT1	1.220	0.858–1.733	0.268
Operative procedure (limited resection)	Lobectomy	1.126	0.756–1.679	0.559
Nodal dissection (ND2)	ND0-1	1.093	0.747–1.598	0.648
Pathological stage (p-stage II or advanced)	p-stage I	2.149	1.471–3.141	<0.0001
Comorbidity (No)	Yes	0.678	0.475–0.966	0.032

HR, hazard ratio; CI, confidence interval; ND2, ND1 plus mediastinal lymph node dissection.

TABLE 6. Multivariate Analysis of Postoperative Complications in Clinical Stage I Cases: Logistic Regression Model

Variable	Reference	OR	95% CI	*p*
Factors in the final model				
Nodal dissection (ND2)	ND0-1	2.292	1.056–4.974	0.036
Comorbidity (Yes)	No	5.347	2.451–11.666	<0.0001
Factors not in the final model				
Gender (female)	Male	0.73	0.275–1.939	0.528
Performance status (2 or 3)	0 or 1	2.877	0.103–2.877	0.103
Histology (non-adenocarcinoma)	Adenocarcinoma	1.011	0.431–2.375	0.979
Operative procedure (limited resection)	Lobectomy	0.913	0.337–2.471	0.857
Clinical T (cT2)	cT1	1.455	0.626–3.380	0.384

OR, odds ratio; CI, confidence interval; ND2, ND1 plus mediastinal lymph node dissection.

TABLE 7. Clinical Background of Operative Mortalities

Case	Age	Gender	PS	c-Stage	Comorbidity	Surgery	Nodal Dissection	p-Stage	Postoperative Complications
1	82	Male	1	IA	Smoking, autoimmune disease	Lobectomy	ND2	IA	Cerebral infarction
2	81	Female	2	IA	Cerebro-neural disease	Lobectomy	ND1	IB	Myocardial infarction, pneumonia
3	80	Male	2	IB	Diabetes mellitus	Lobectomy	ND1	IB	Cerebral infarction, pneumonia
4	80	Male	0	IB	None	Lobectomy	ND0	IB	Pneumonia
5	80	Male	0	IB	Smoking, Interstitial pneumonitis	Lobectomy	ND2	IB	Pulmonary embolism

ND, lymph node dissection; ND0, without lymph node dissection or lymph node sampling; ND1, intrapulmonary and hilar lymph node dissection; ND2, ND1 plus mediastinal lymph node dissection; PS, Performance status.

better long-term survivals.[7,8,18] There are several possible reasons for these differences. First, this study was limited to preoperative stage I patients. Second, the number of patients with a large tumor (≥50 mm in diameter) was less than that in the report citing lower survival rates.[10] Third, as expected from the country with the world's highest life expectancy (78.5 years for men and 85.5 years for women[2]), Japanese octogenarians may have better physiological and medical conditions in comparison with the elderly in other countries.

A multivariate analysis identified p-stage and comorbidity status as significant factors influencing long-term survival. Although p-stage is a well-known prognostic factor, the role of comorbidity in prognosis is less clear.[19,20] Any discussion of prognostic factors should consider that lung cancer-related deaths accounted for only 76 (52.1%) of the 146 deaths recorded in this study. Thus, comorbidity might influence the risk for death from causes other than lung cancer in elderly patients, as previously studied by Charlson et al.[21] Of note, the 5-year lung cancer-specific survival rates in this study (77.9% for c-stage IA and 66.9% for c-stage IB) were almost equivalent to those for the general population in Japan.[14,17] Surgeons should therefore consider comorbid diseases and preoperative staging in selecting those elderly patients most likely to achieve long-term benefit from pulmonary resection.

Postoperative complications were observed in 8.4% of the patients in this study. Comorbidity and mediastinal lymph node dissection (ND2) were identified as risk factors for increased postoperative complications by the multivariate analysis. Previous studies in elderly patients also proposed mediastinal lymph node dissection as a risk factor for postoperative complications.[22,23] From the surgical point of view, recurrent nerve exposure, devascularization of the bronchial wall, and increased surgical exudates or bleeding due to mediastinal lymph node dissection are thought to be associated with several possible complications. However, this procedure is necessary for a complete resection in the patients with subclinical nodal diseases, accounting for 14.4% of the cohort in this study. Recently, advanced technologies such as 2-fluoro-2-deoxyglucose-positron emission tomography and endobronchial ultrasound-guided transbronchial needle aspiration have been available to evaluate hilar and mediastinal lymph nodes. These modalities could help in selecting the patients who can be cured without mediastinal lymph node dissection. In this regard, a more accurate preoperative staging may facilitate to decrease the postoperative complications.

The recommended surgical treatment for c-stage I patients is lobectomy and mediastinal lymph node evaluation.[5] However, a limited resection and a lesser extent of lymph node dissection (ND0-1) were commonly performed in this study (limited resection in 33.2% and ND0-1 in 65.4% of patients) in comparison with the general population (limited resection in 4.7% and ND0-1 in 11.9%[14]). Although the reasons for selection of these procedures by the surgeons were not recorded in the registry, it is assumed that the surgeons intended to reduce the perioperative risks. Interestingly, the present study found no significant difference in the long-term survival of elderly patients between those who

underwent limited resection and lobectomy. This conflicts with a previous study from the Japan Lung Cancer Registry suggesting that lobectomy or pneumonectomy was a predictor of a good outcome for patients with stage I cancer in the general population.[14] According to data from The National Cancer Registry in the United States,[24] lobectomies confer a significant survival benefit over limited resections, except in patients >71 years of age. Taken together, these findings implicate limited resection as an important alternative treatment for elderly patients with early-stage lung cancer despite lobectomy still being the ideal surgical option when the patient can tolerate the procedure. Consequently, minimizing surgical intervention in terms of both pulmonary resection and lymph node dissection should be considered to treat elderly patients with early-stage NSCLC as long as complete resection could be performed.

The operative mortality rate of 1.4% in this study was lower than those cited in recent studies with large sample sizes that described hospital mortality/30-day hospital mortality ranging from 2.2 to 8.8%.[8,20] The rate in this study is also comparable with the mortality rate of lung cancer resection in the total population.[17,25] Possible reasons for this low-mortality rate include the lower rate of patients with comorbid diseases and the higher proportion of patients undergoing less invasive surgery in this study.

Nonsurgical local therapies are currently used in the treatment of stage I lung cancer.[26–29] In most cases, these therapies are indicated for high-risk patients unfit for surgery. Furthermore, recent technological advances have greatly improved the long-term results of these modalities with low treatment-related mortality. The benefits and the morbidity of surgery need to be carefully weighed against these less invasive approaches, especially in elderly patients. At present, there is little information available on comparison of these modalities with surgery with respect to overall survival rates and disease recurrence.[30] A clinical trial comparing the short- and long-term results of these different modalities would reliably help future surgical decision making with regard to treatment of local lung cancer in the elderly. Until such studies are performed, the results obtained in the present surgical series may constitute a basis on which to compare results.

The strengths of this study include the large sample size, the nationwide multi-institutional nature of the data, homogenous oncological status, minimum patients lost to follow-up, and the availability of complete pathologic findings. Limitations were that the study was retrospective, and that comorbidity status and postoperative complications were not described in detail. Several objective measurements can be used to evaluate and describe comorbidity and complications, as used in various previous studies.[19,31–33] Such scoring systems enable comparison of the results among studies involving different patient backgrounds and treatment modalities. Activity of daily living and quality of life after surgery, not evaluated in this study, are also very important concerns for elderly patients and their family to consider when deciding to undergo surgery. In addition, the smoking history was not taken. If a patient quit smoking 1 month before surgery, the patient was categorized into a group of nonsmokers. This was the reason why the percentage of current smokers was low (10.7%).

In summary, the long-term results of c-stage I NSCLC in octogenarians were satisfactory, with a 5-year survival rate of 55.7% for c-stage I, 62.0% for c-stage IA, and 47.2% for c-stage IB. Pathologic stage II or higher cancer and the presence of comorbidity were significantly independent factors predicting short survival, whereas comorbidity and mediastinal lymph node dissection (ND2) were independent risk factors for postoperative complications.

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Solitary pulmonary metastasis of mucoepidermoid carcinoma of the palate 43 years after the initial treatment

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Case report - Thoracic oncologic

Solitary pulmonary metastasis of mucoepidermoid carcinoma of the palate 43 years after the initial treatment

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Abstract

This report describes the case of a 71-year-old female presenting with a metastatic mucoepidermoid carcinoma (MEC) in the lung 43 years after the initial treatment for the primary tumor. This case represents a very long period between initial diagnosis and distant metastasis with a pathological examination of both the primary and metastatic tumors. Metastatic tumor should be considered for the differential diagnosis of a pulmonary nodule in a patient who has a history of this type of oral tumor.

Keywords: Histology (mucoepidermoid); Metastasis

1. Introduction

In 2007, a 71-year-old female was admitted to the hospital for further evaluation of single 16 mm pulmonary nodule in the right lower lobe (Fig. 1), which was detected on a screening chest CT to assess a slight chest discomfort. Surgery was performed, based on the suspicion of lung cancer. The intra-operative pathological diagnosis revealed that the tumor was malignant, but no definitive diagnosis could be obtained. Therefore, a lower lobectomy was performed as a standard procedure for primary lung cancer. Macroscopically, the resected tumor was firm and white with a well-defined edge.

The past medical history indicated a malignancy in the oral cavity. In 1964, the patient presented with a small (~5 mm), firm, and painless swelling on the palate at the age of 32. The patient underwent a local tumor excision at a primary care physician without pathological diagnosis. A 5 mm tumor recurred at the same place in 1967, and the patient underwent a re-excision at a cancer hospital. The tumor was pathologically diagnosed as mucoepidermoid carcinoma (MEC) of the palate. In 1970, the tumor recurred again at the same place. The patient underwent an extended tumor resection including bone and palate. Since then, the patient has been healthy without any recurrence.

Hematoxylin-eosin staining of the specimen showed non-keratinizing squamoid cells with ample eosinophilic cytoplasm that grew in a trabecular pattern and scattered mucous cells were observed with PAS staining (Fig. 2a, b). Suspecting a metastatic MEC, the tumor sample resected in 1970 was obtained and compared to the pulmonary nodule. The cellular and histological appearance of the oral tumor was identical to the pulmonary nodule (Fig. 2c, d). In addition, both tumors were positive for CK34bE12 but negative for CK7 or CK20. Based on these findings, the lung tumor was diagnosed as a solitary metastasis from the MEC in the oral cavity 43 years after the initial treatment. No additional treatment was offered, and the patient remained healthy for 24 months.

2. Comment

MEC is the most common salivary gland malignancy [1]. Approximately, half of tumors occur in minor salivary gland, especially in the palate. Most patients with this disease have a favorable outcome after a complete resection [2, 3]. However, the disease may recur in distant organs in a small subset of the patients during long-term follow-up periods. A review of 173 salivary gland MECs [3] noted that distant metastases affected 16 patients (9.2%), most frequently in the lungs. Although late recurrence is not rare in MEC, this case had an exclusively long interval between the initial treatment and distant metastasis. Furthermore, this is thought to be the longest interval among the case reports where a histological examination for both primary and metastatic tumor could be performed.

MEC is characterized by squamoid, mucus producing and cells of an intermediate type. MECs are usually classified as low-, intermediate-, or high-grade malignancies based on the histological variables including necrosis, mitosis, perineural invasion, and dominant type of cells [1, 4]. This case was classified into an intermediate-grade malignancy. From the clinical point of view, the repeated local recurrences suggest that the malignant potential of this disease is relatively high.

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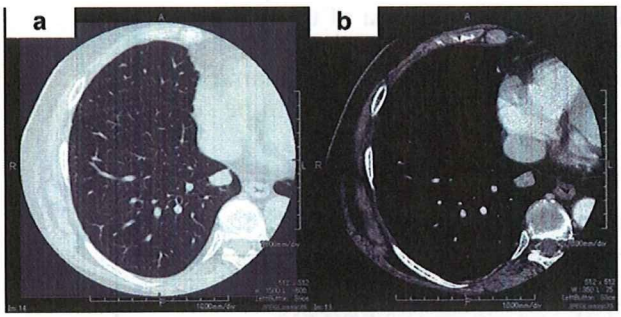

Fig. 1. Chest computed tomography shows a 16 mm nodule in the right lower lobe.

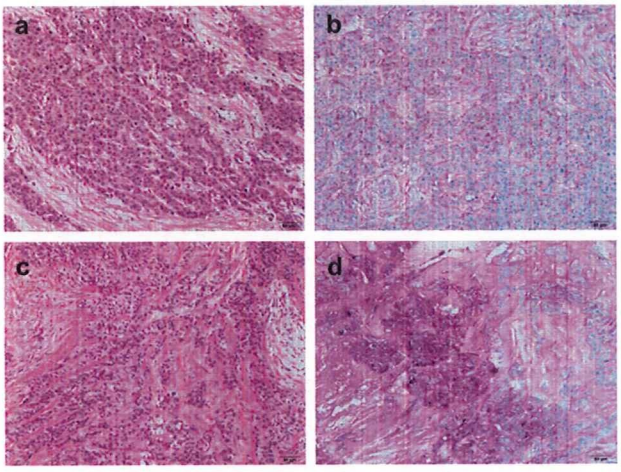

Fig. 2. Pathological findings of the pulmonary nodule [(a) and (b)] and primary tumor [(c) and (d)]. Hematoxylin-eosin staining revealed mucoepidermoid carcinoma of the palate (c) and similar histological appearance in the pulmonary nodule (a). PAS staining showed typical mucus containing cells in the primary tumor (d) and the metastatic tumor (b).

Besides the salivary glands, the lung is one of the primary sites where MEC may develop [5]. However, most of the pulmonary MECs arise from bronchial glands in the central airways. Since the tumor in this case was located in peripheral lung parenchyma with clear defined margin, the disease was diagnosed metastatic MEC.

The question when the tumor began to grow and formed a metastatic lesion is interesting but cannot be answered. Tumor cells might have been disseminated and present in the lung when the primary and local recurrent tumor was treated. This kind of phenomenon is often explained by cancer dormancy, in which residual disease is present but remains asymptomatic or undetectable [6]. Although the precise mechanism of this hypothesis remains poorly understood, various factors have been identified as possible contributors.

In summary, a metastatic tumor should be considered for the differential diagnosis of a pulmonary nodule in a patient who has a history of this type of oral tumor.

Acknowledgments

We would like to thank to Dr Mamoru Morita (Head and Neck Surgery, Jichi Medical University Hospital, Tochigi) and Dr Kazuyoshi Kawabata (Division head of Head and Neck Surgery, Cancer Institute Hospital, Tokyo) who kindly provided clinical information and unstained slides of primary lesion and Dr Genichiro Yoneda (Sakai municipal hospital) for pathological examination.

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Interactive CardioVascular and Thoracic Surgery

Case Report

A Case Report of Large Thymic Hyperplasia Associated with Hyperthyroidism

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A 32-year-old female case of large thymic hyperplasia with hyperthyroidism is reported. A computed tomography (CT) examination disclosed a large mediastinal mass (16 × 11 cm) with a heterogeneous internal structure containing both soft tissue density areas and fat density areas. The mass was histologically diagnosed as thymic lymphoid hyperplasia. The thymic mass enlarged during hyperthyroidism and then regressed markedly after treatment with antithyroid drugs. After the thymic mass decreased by about one third of its maximum volume, the mass stopped regressing and has remained the same size for more than 6 years. A CT scan showed a decrease in the soft tissue density area and predominance of the fat density area. The potential response to antithyroid therapy must be considered before recommending resection of thymic tumors diagnosed as hyperthyroidism-related thymic hyperplasia. (Ann Thorac Cardiovasc Surg 2009; 15: 404–407)

Key words: thymic hyperplasia, hyperthyroidism, thymolipoma

Introduction

Although benign thymic hyperplasia (BTH) is a known feature of hyperthyroidism,[1)] this is infrequently appreciated by clinicians. Surgical resection is a common approach to an anterior mediastinal mass, whereas recognition of the benign nature of BTH would prevent a major surgical procedure.[2)] Although several reports have described regression of the anterior mediastinal mass following treatment of hyperthyroidism, according to our literature survey, this is the first paper to report that a thymic hyperplasia increased during hyperthyroidism and regressed as thyroid function normalized. Among the cases of thymic hyperplasia with hyperthyroidism reported to date, the present case is the largest that has regressed as a result of treatment for Graves' disease.

Case Report

A 32-year-old female noticed edema of her bilateral lower limbs and consulted our hospital. A chest X-ray revealed a large anterior mediastinal mass without chest symptoms (Fig. 1A). She was found to have symmetrical diffuse enlargement of the thyroid gland, tachycardia, and heavy perspiration. A thyroid function test demonstrated free thyroxine (free T4) to be 6.4 ng/dl (normal: 0.8–2.1 ng/dl), free triiodothyronine (free T3) to be 14.2 ng/dl (normal: 3.2–5.7 ng/dl), thyroid stimulating hormone (TSH) < 0.01 uU/ml (normal: 0.3–5.0 uU/ml), TSH receptor antibody (TR-Ab) at 48% (normal: 0%–9%), thyroglobulin passive agglutination (TGPA) test < 100 (normal: 0.5–100.5), and microsome passive agglutination (MCPA) test at 400 (normal: 0.5–100.5). These findings were consistent with Graves' disease.

A chest computed tomography (CT) scan showed a

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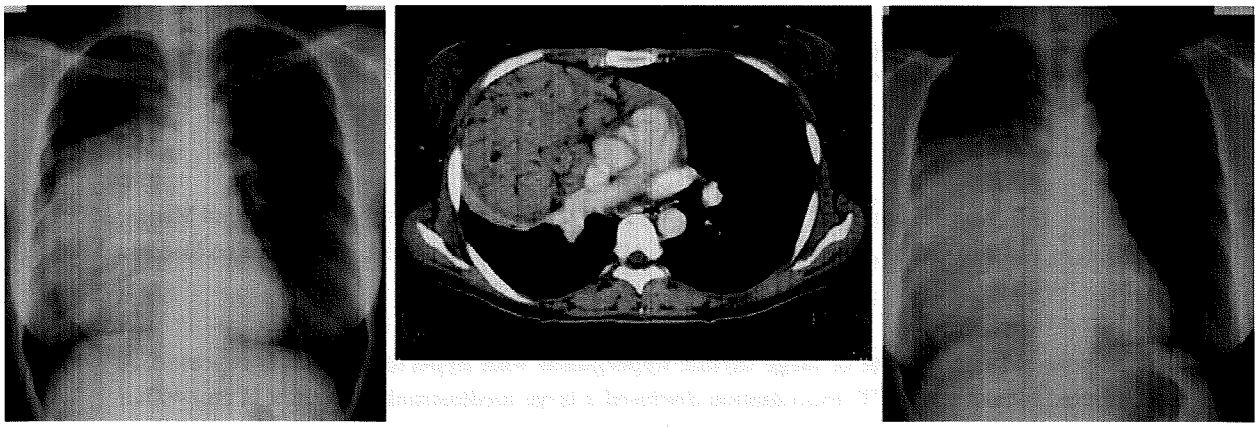


Fig. 1.
A: A posteroanterior chest radiograph taken on admission showing a large mass in the right anterior mediastinum.
B: A chest CT scan (mediastinal window) showing 16 × 11 cm lobulated soft tissue attenuation in the lesion separated with fat attenuation in the mass.
C: During the uncontrolled hyperthyroid period, the anterior mediastinal mass enlarged to 17 × 12 cm in size.

16 × 11 cm mass composed of a complex mixture of soft tissue density areas and fat density areas on the right side of the anterior mediastinum. The soft tissue area was predominant and was separated with a meshlike structure of fat density areas. The lesion of soft tissue density was slightly enhanced with contrast medium (Fig. 1B). The middle lobe of the right lung was compressed by the huge mass, resulting in atelectasis. It was clinically diagnosed that this huge mediastinal mass was a thymic hyperplasia associated with hyperthyroidism.

Treatment with thyamazol was started. However, thyamazol caused severe nettle rash, so the antithyroid drug was switched to propylthiouracil. For the first month of treatment, the hyperthyroidism was not well controlled. During this period, the mediastinal mass increased in size (Fig. 1C). An anterior mediastinotomy biopsy was performed to confirm a definitive diagnosis. Pathological examination with hematoxylin-eosin, Mic2, and CD79a showed an increased number of lymphoid follicles with germinal center formation, largely composed of B lymphocytes (Fig. 2), and also an increased number of Hassall's corpuscles with keratin stain. The large mediastinal mass was histologically diagnosed as thymic lymphoid hyperplasia.

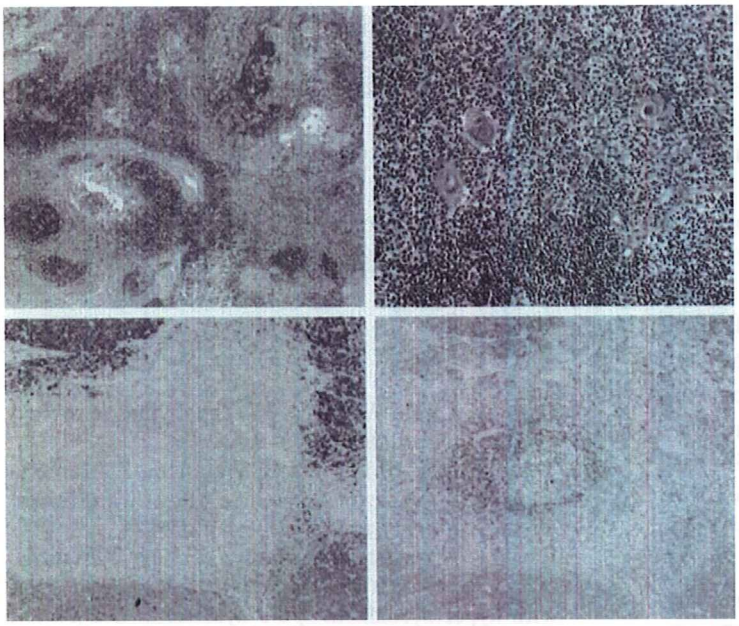
As the hyperthyroidism was normalized with propylthiouracil, the thymic hyperplasia began to decrease in size. After 19 months of treatment with antithyroid drugs, the volume of the thymic mass decreased to 34% of its maximum. A chest CT scan showed a decrease in the soft tissue attenuation component and a relative increase in the fatty tissue attenuation component (Fig. 3). Although thyroid function remained normalized, the mass did not regress further in the subsequent 6 years.

In July 2003, the patient experienced normal pregnancy and delivery. Thyroid function was well controlled within the normal range, and no size or structural change of the mass was observed during the perinatal period.

Discussion

Histological examination of Graves' thymic glands has disclosed lymphoid follicle proliferation (thymic hyperplasia) in approximately one third of patients.[1] Moreover, the enlarged thymus was shown to regress as a result of hyperthyroidism treatment with an antithyroid agent.[3–5] Also in animals, thyroidectomy was followed by thymic involution.[6] The possible existence of a thymic thyrotropin receptor that acts as an autoimmune antigen in patients with Graves' disease has been demonstrated.[7] TR-Ab and expression of the thyrotropin receptor in the thymus may play a principal role in the development of thymic hyperplasia in Graves' disease.

Although anecdotal case reports indicate that thymic enlargement or thymic hyperplasia is associated with Graves' disease, about half of them were reported after surgical resection of the thymic mass.[2] Although BTH has been shown to regress following treatment of hyperthyroidism, median sternotomy and surgical resection is a common approach for anterior mediastinal masses because thymic



A | B
C | D

Fig. 2. Microscopic findings of the mass.
A: An increased number of lymphoid follicles with germinal center formation is present. (HE: ×16)
B: An increased number of Hassall's corpuscles is present. (HE: ×50)
C,D: Pathological examination with Mic2 (C) and CD79a (D) showing lymphoid follicles with germinal center formation, which are largely composed of B lymphocytes. (×25)

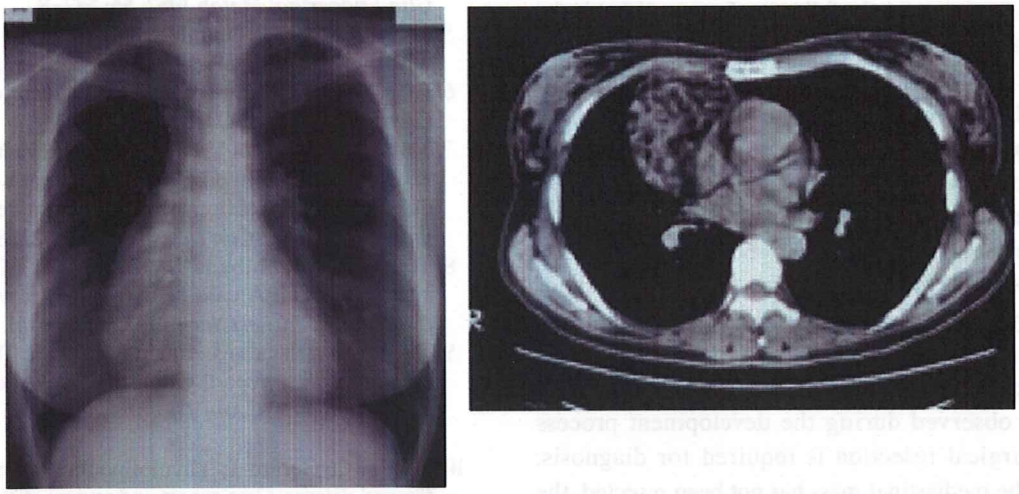


Fig. 3. A chest radiograph **(A)** and CT scan **(B)** showing a significant decrease in the size of the mass. Involution of the soft tissue attenuation area is marked. As a result, the fatty tissue attenuation component is predominant.

A | B

neoplasms or other malignancies cannot be completely excluded. Recognition of the association of thymic hyperplasia with hyperthyroidism and its benign course following treatment for hyperthyroidism would contraindicate a major surgical procedure. Therefore in cases with a nonspecific anterior mediastinal mass, screening of the thyroidal function is essential. If hyperthyroidism is proved without malignant signs, the clinician should consider observation of the anterior mediastinal mass with the administration of antithyroid drugs. Differential diagnosis of an anterior mediastinal mass should be carefully done because it may include malignant entities, such as thymic cancer, germ cell tumors, and malignant lymphoma. Thymic hyperplasia in Graves' disease has a benign nature