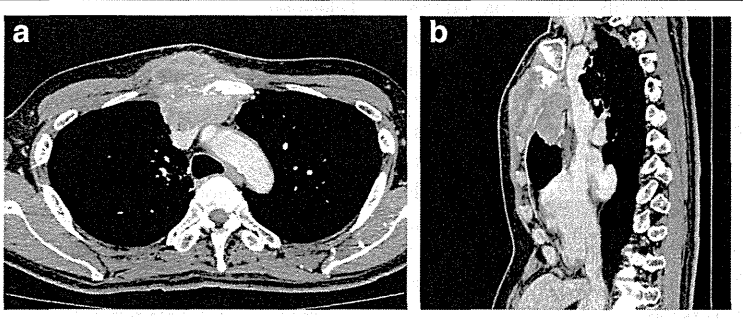

Figure 1 The computed tomographic scan showed an anterior mediastinal tumor penetrating into the sternum. (a) Horizontal section; **(b)** sagittal section.

Tumor cells are round to oval with eosinophilic cytoplasm. The nuclei of tumor cells are bizarrely shaped with prominent nucleoli. Parietal involvement was positive, but histological invasion of the tumor cell into pulmonary parenchyma was not observed. The result of immunohistochemical investigations were that CEA was positive but thyroglobulin, BER-EP4, CD56, chromogranin A, and synaptophysin were negative. Based on these findings, the primary thymic papillary adenocarcinoma was diagnosed. The disease was described at stage III (T3N0M0) according to Weissferdt-Moran TNM Staging System for Thymic Carcinoma [1] and also at the same stage by Masaoka staging system for thymoma. Any adjuvant therapy was performed for this patient because there is no evidence-based treatment for thymic carcinoma after the tumor is completely resected. The patient has been free of disease for 36 months after surgery without any other treatment.

Discussion

Thymic carcinoma is relatively uncommon among thymic epithelial tumors, constituting approximately 10% of these lesions [2]. While most of them are squamous cell carcinoma, papillary carcinoma, one of the subtypes of thymic adenocarcinoma, is an exceedingly rare tumor and was first described in 1998 [3]. According to the histological study of 65 patients with thymic carcinoma, papillary carcinoma represents only 2 cases (3%) [4]. Recently, two of the cases with papillary thymic adenocarcinoma have been reported. One developed in a thymic cyst [5] and the other one was incidentally found in the resected specimen of type AB thymoma [6]. Contrary to the thymus, the papillary morphology is common in other organs. For differential diagnosis, the possibility of a metastatic papillary carcinoma or a papillary carcinoma in an ectopic thyroid gland should be excluded. In this case, following negative immunohistochemical staining for thyroglobulin and no subsequent malignant disease after surgery, we have confirmed the diagnosis. The clinical features and the treatment outcomes of thymic papillary carcinoma have not been well described yet. The limited available reports indicate that five out of eight cases developed recurrences at local site or as pleural dissemination within 2 years of surgery [7]. The remarkable elevation of serum CEA value, which was observed in this case, did not seem to be common in papillary thymic carcinoma in the literature, while positive immunoreactivity of this antigen was sporadically reported [3]. More cases need to be accumulated to define the clinical features of this type of thymic carcinoma.

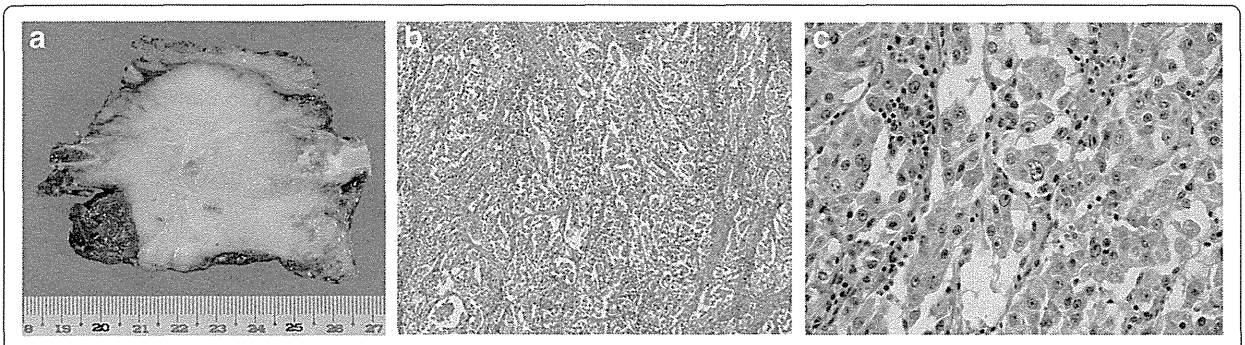

Figure 2 A gross specimen of the thymic tumor (a) and pathological findings (Hematoxylin and eosin stain, original magnification x40 for b and x200 for c).

Not only for the rarity of the histology, the current case was characterized for the highly aggressive invasiveness to the sternum. The tumor destroyed the sternum and the costal cartilages with osteolytic change and reached subcutaneous fat tissue. Interestingly, any other adjacent organs such as great vessels, pericardium, and lung were not involved. As long as we searched similar cases in the literature, there was a case with thymic carcinoma minimally invading into the sternum [8]. However, it seemed to be rare that this disease represents the massive sternal invasion as seen in this case.

Resection of the sternum often requires skeletal and/or soft tissue reconstruction with artificial materials or a muscle flap. We discussed this issue with a plastic surgeon preoperatively and planed a pectoralis major muscle flap for an anterior chest wall reconstruction if it was necessary. Consequently, reconstruction was not indicated in this patient because sufficient stability and rigidity of the chest wall were maintained.

Conclusion

We described the clinical and pathologic features of this extremely rare thymic papillary adenocarcinoma that invaded into subcutaneous tissue penetrating the sternum.

Consent

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

Abbreviations

CT: Computed tomography; FDG: 18 F-fluorodeoxy glucose; PET: Positron emission tomography; CEA: Carcino-embryonic antigen; AFR: Alpha-fetoprotein; beta-HCG: Beta-human chorionic gonadotropin; SCC: Squamous cell carcinoma antigen.

Competing interests

The authors have declared that no conflict of interests exists.

Authors' contributions

IY analyzed and interpreted the patient data. JO performed the literature review, and was a major contributor in writing the manuscript. YT made a pathological diagnosis and prepared pathological figures. AF, TT, and TK helped surgery, encouraged to complete the work. MH supervised the data and the final editing of the manuscript. All authors read and approved the final manuscript.

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INTERNAL MEDICINE

□ CASE REPORT □

Porous Diaphragm Syndrome with Repeated Rapid Accumulation of Pleural Effusion

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Abstract

A 53-year-old woman was admitted with right massive transudative pleural effusion and acute renal failure. The amount of pleural fluid reduced in response to treatment with hydration and diuretics; however, the effusion recurred one month later. We suspected the presence of a right pleuroperitoneal communication allowing pleural fluid to accumulate from an origin of ascites triggered by renal failure. Chest computed tomography following pleural drainage revealed a small nodule in the right upper lobe of the lung. A diagnosis of T1aN0M0 lung adenocarcinoma was made based on the results of various examinations, including bronchoscopy. Video-assisted thoracoscopic surgery was performed, and the presence of a small hole communicating between the pleural and peritoneal cavities was confirmed in the right diaphragm during the surgery.

Key words: porous diaphragm syndrome, acute renal failure, lung cancer

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(DOI: 10.2169/internalmedicine.53.1444)

Case Report

A 53-year-old woman was admitted to our hospital due to progressive respiratory distress, pain in the chest and left lower quadrant of the abdomen and bilateral leg edema. At 43 years of age, she had undergone total hysterectomy and postoperative radiation for stage 1b cervical cancer. Since that time, she had experienced symptoms of depression and began to take antipsychotic drugs. The laboratory data on admission revealed an increased inflammatory reaction, renal dysfunction and hyponatremia (Table). Computed tomography (CT) showed right massive pleural effusion resulting in a mediastinal shift and a small amount of ascites (Fig. 1). The pleural fluid obtained via thoracentesis was transudative, although the levels of carcinoembryonic antigen (CEA) and adenosine deaminase activity (ADA) in the fluid were not elevated. No bacteria or cancer cells were detected. The results of an echocardiogram were normal, ruling out the possibility of congestive heart failure. Hydration therapy was initiated for renal failure, and the pleural effusion was drained continuously via a chest tube. The pleural effusion decreased in size spontaneously, even after removal of the drainage tube, and the patient was discharged. CT performed after the drainage therapy showed a solitary pulmonary nodule measuring 15 mm in diameter with spiculation in the right upper lung. Bronchoscopy was performed, which revealed adenocarcinoma cells. On 18F-FDG PET/CT (positron emission tomography/CT), abnormal 18F-fluorodeoxyglucose (18FDG) accumulation was observed only in the nodule, not in the right pleura. Since malignant pleural disease was unlikely, we made a diagnosis of stage IA lung cancer. Although stereotactic body radiotherapy was planned for the lung cancer based on the patient's request, sudden dyspnea and pain in the left lower abdomen developed approximately one month after discharge. Chest radiography showed massive right pleural effusion, and serum biochemistry again demonstrated renal dysfunction. Hydration therapy was administered, with an infusion of 1,500 mL/day; however, the urinary volume remained under 400 mL/day and the pleural effusion rapidly increased in size. Postrenal failure was suspected, and a urinary duct was in-

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Table. Laboratory Data on Admission

Casual blood count		Biochemistry		Tumor Marker	
RBC	484×10^4/mm^3	TP	7.3 g/dL	SCC	0.6 ng/mL
Hb	14.9 g/dL	Alb	4.5 g/dL	CEA	3.3ng/mL
Hct	40.3 %	T-Bil	0.7 mg/dL	CA125	54U/mL
WBC	13670 /mm^3	AST	25 IU/L	CA19-9	26U/mL
Neut	86.8 %	ALT	15 IU/L		
Pl t	44.2×10^4/mm^3	LDH	247 IU/L	Pleural effusion	
		ALP	324 U/L	Color light yellow	
Serology		CPK	255 U/L	Cells 992/mm3	
CRP	6.2 mg/dL	BUN	26mg/dL	Specific Gravity 1.016	
		Crtn	2.6 mg/dL	TP 1.4g/dL	
H-BNP <12.4		Na	121mEq/L	Alb	<1.0g/dL
HANP 41.2pg/mL		K	4.3 mEq/L	LDH	168U/L
ADH 41.2pg		Cl	90 mEq/L	Glu	99mg/dL
		Ca	7.6mg/dL	ADA	6.9U/L
				Na	123mEq
				K	5.3mEq
				Cl	95mEq
				CEA	0.8ng/mL

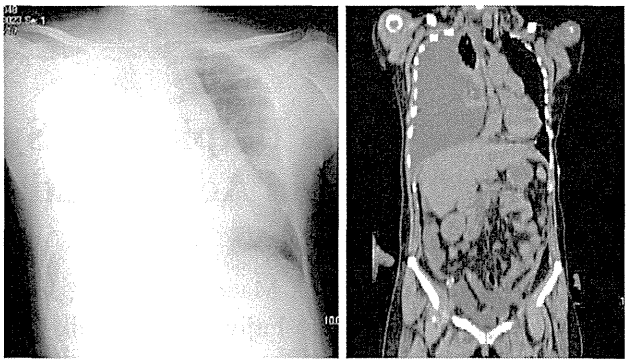


Figure 1. A chest radiograph showing massive right pleural effusion (a). Thoracoabdominal computed tomography (CT) showed right pleural effusion, mediastinal shift and a small amount of ascites (b).

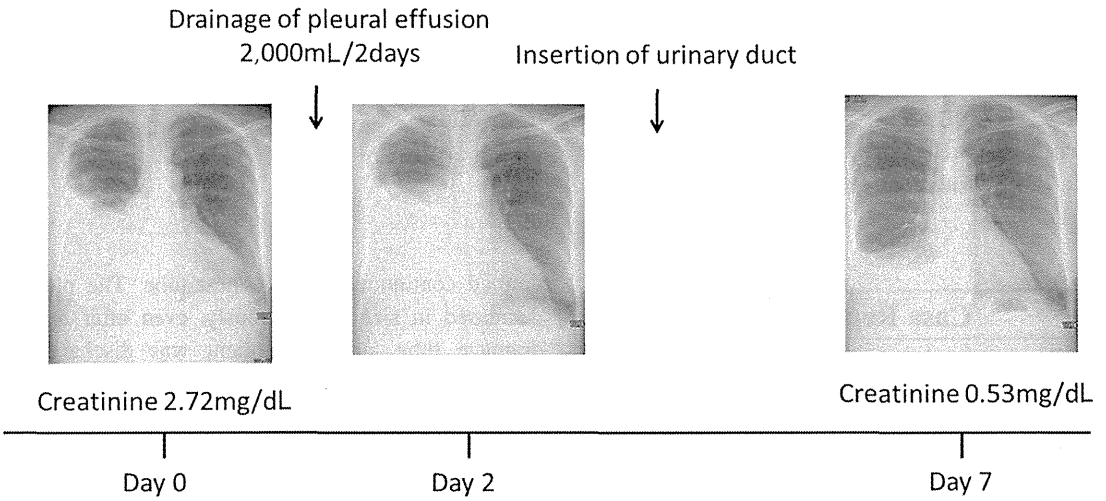


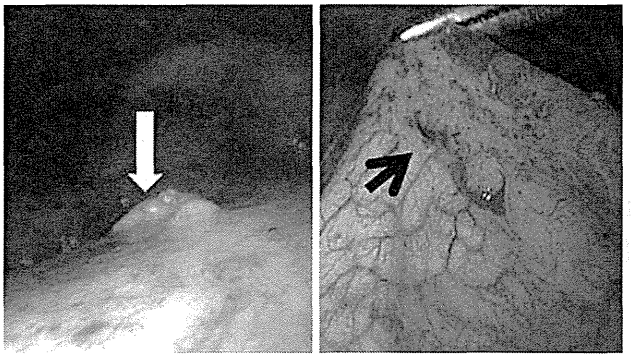
Figure 2. Clinical course of the patient during the second hospitalization

serted. The urinary volume subsequently increased to over 2,000 mL a day, and the pleural effusion improved following the insertion of a urinary duct (Fig. 2).

The pleural effusion was transudative and appeared only on the right side on both occasions. In addition, it repeatedly accumulated very rapidly and was accompanied by renal insufficiency. A diagnosis of malignant pleural effusion was unlikely. Because we found no abnormalities in the right thorax that could be the cause of the pleural effusion, except for the T1aN0M0 lung cancer, we suspected that the pleural effusion derived from ascites via a right-sided pleuroperitoneal communication. Urinary retention resulting in repetitive acute renal failure appeared to be the underlying trigger. Urodynamic testing revealed no stenosis of the urinary tract, and we suspected that the patient's postrenal dysfunction was caused by the antipsychotic drugs she received for depression (olanzapine, quetiapine fumarate and mirtazapine), which may have triggered renal failure. Video-assisted thoracoscopic surgery was performed for the lung cancer. Upon inspection of the entire thoracic cavity during the surgery, a small pore was detected in the central tendon of the right diaphragm (Fig. 3). Direct closure of the pore was performed, which successfully stopped the leakage. The sT1aN0M0 lung cancer lesion was resected without pleural dissemination.

Discussion

Pleural effusion is a common clinical problem with many different etiologies that sometimes requires complicated strategies for diagnosis (1, 2). Because our patient had lung cancer in the right upper lobe, pleural metastasis of lung



a b

Figure 3. A bleb was located in the center of the right diaphragm (a, white arrow). After removing the bleb, a pore was identified (b, black arrow).

cancer was a reasonable cause of the pleural effusion. Pleural recurrence of cervical cancer was another possibility; however, several lines of evidence excluded this option, including the lack of signs of pleural metastasis on CT (3), the transudative nature of the effusion, the rapid and repetitive accumulation of pleural fluid and the absence of malignant cells in the pleural fluid obtained three different times. The sensitivity of pleural fluid cytology is reported to range between 40% and 87%, with a mean of approximately 60% (1), in patients with malignant pleural effusion. The occurrence of transudative effusion is typically ascribed to the presence of extrapleural systemic factors, such as increased hydrostatic pressure in the systemic or pulmonary capillaries and decreased colloid osmotic pressure in the systemic circulation. However, transudative pleural effusion is generally bilateral, unless there is a unique cause of unilateral accumulation, such as pleural adhesion (3). No signs of left pleural adhesion were observed in the present patient.

These results indicate that it is difficult to ascribe cases of effusion to thoracic abnormalities. In the present case, we suspected a peritoneal origin of the effusion and the presence of pleuroperitoneal passage, referred to as "porous diaphragm syndrome" (4). In this syndrome, effusion is predominantly observed on the right side. This laterality is explained by the "peritoneal circulation" (5) and "piston-like action" between the right hemidiaphragm and liver (6). Pathologically, a hole originates from a small defect in the tendinous portion of the diaphragm in association with bleb or blister formation. The pressure of ascites impacts the diaphragm, thinning and finally rupturing these structures, resulting in a one-way pathway from the abdominal cavity to the thoracic cavity (7). Therefore, massive pleural effusion can occur, despite the presence of only a small amount of ascites, as observed in the present case.

The authors state that they have no Conflict of Interest (COI).

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CASE REPORT

A possible abscopal effect of post-irradiation immunotherapy in two patients with metastatic lung tumors

Ken Kodama · Masahiko Higashiyama · Jiro Okami · Toshiteru Tokunaga · Norimitsu Inoue · Takashi Akazawa · Tsukasa Seya

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Abstract As well as its local effects, radiotherapy leads to the delayed regression of distant non-irradiated lesions. These abscopal effects are most likely mediated by the innate immune system. Patient 1, a 74-year-old male, had concomitant left supraclavicular lymph node metastases and multiple lung metastases 2 years after complete resection of pathological stage IIA (T1bN1M0) lung adenocarcinoma. He received radiation therapy (RT) of 58 Gy for the supraclavicular lymph node metastases and then innate immunotherapy using the cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin (BCG-CWS). Three months after the RT and 2 months after the immunotherapy, all lung metastases disappeared on computed tomography scans. Patient 2, a 40-year-old female, underwent stereotactic body RT (SBRT) for metastasis from a deep-seated urothelial carcinoma in the right upper lobe of the lung. Twenty-one months after the SBRT, we started administration of BCG-CWS to two new lesions that had appeared in the left lung. As a result, after 3 months, the lesions completely disappeared. Complete response was maintained for more than 1 year in both patients. We believe that an optimal combination of RT and immunotherapy will elicit abscopal effects that can be employed to attain a systematically achievable, rather than anecdotal, therapeutic goal.

Keywords Abscopal effect · Radiation therapy · Innate immunotherapy · Metastatic lung tumor

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Introduction

The word "abscopal" is derived from the Latin words *ab*, meaning "position away from," and *scopos*, which means "a target for shooting at." Mole was the first to use this term in 1953 [1] to describe systemic effects that were observed at non-irradiated sites in an animal after treatment with localized radiotherapy (RT). Case reports describing abscopal effects observed after RT have been published for a variety of malignancies, including urothelial carcinoma, lymphoma, esophageal adenocarcinoma, hepatocellular carcinoma (HCC), uterine cervical carcinoma, thymic carcinoma, chronic lymphocytic leukemia, and melanoma [2–12]. Abscopal effects are usually associated with radiotherapy, but they are also sometimes seen after other treatments, such as surgery or even hyperthermia.

We experienced two cases with possible abscopal effects in which local RT followed by innate immunotherapy using the cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin (BCG-CWS) [13] were associated with the regression of metastatic lung cancers at a distance from the irradiated site.

Case presentations

Patient 1

A male patient received a diagnosis of lung adenocarcinoma in January 1997 at 74 years of age. His clinical course is shown in Fig. 1. He underwent right upper lobectomy with hilar and mediastinal lymph node dissection. Pathologic examination revealed T1bN0M0, stage IIA adenocarcinoma. He remained disease-free until November 1998, when a 20-mm-diameter lymph node was palpable in the left supraclavicular region and a chest computed tomographic (CT) scan revealed swelling of the lymph nodes and new multiple pulmonary nodules less than 10 mm in diameter. Metastatic adenocarcinoma was proven by percutaneous needle aspiration cytology of the lymph node.

For this elderly patient, who refused systemic chemotherapy, RT was initiated to the supraclavicular lymph node metastases, with 48 Gy supplied in 24 fractions plus a 10 Gy boost to the nodular lesion from 5 January to 17 February 1999.

After fully discussing the risks and benefits with his physicians and obtaining informed consent, the patient enrolled in a clinical phase II study on innate immunotherapy using BCG-CWS at Osaka Medical Center for Cancer and Cardiovascular Diseases [14]. The institutional review board of the Osaka Medical Center for Cancer and Cardiovascular Diseases approved this study in 1994. From 29 March 1999, he received intradermal inoculation of BCG-CWS at a dose of 200 μg every week, for a total of 4 doses, as part of induction therapy. The immunotherapy was then continued at a dose of 100 μg every 4 weeks as maintenance therapy until January 2001. The serum interferon-gamma (IFN-γ) values measured three times at 1-month intervals were 25.5, 70.4, and 1770 pg/ml (normal range <7.8 pg/ml), respectively.

Up to April 1999, the lymph node metastases were palpable and then decreased in size, finally becoming impalpable at the end of May 1999, after 4 doses of BCG-CWS. In August 1999, a CT scan showed the complete response of not only the irradiated lymph node metastases but also multiple pulmonary metastases.

He remained disease-free until June 2003. In May 2004, a CT scan showed a new lesion of size 50 × 20 mm in the left upper lobe of the lung. Cytological findings following bronchoscopy revealed adenocarcinoma. No definitive diagnosis as to whether it was a second primary or metastatic lesion was made. We started the oral administration of gefitinib at 250 mg/day. As a result, a good response was achieved, and this was maintained from August 2004 to the beginning of 2006. In July 2006, the tumor showed enlargement and was hypermetabolic on positron-emission tomography (PET), with a standard uptake value of 4.4. For

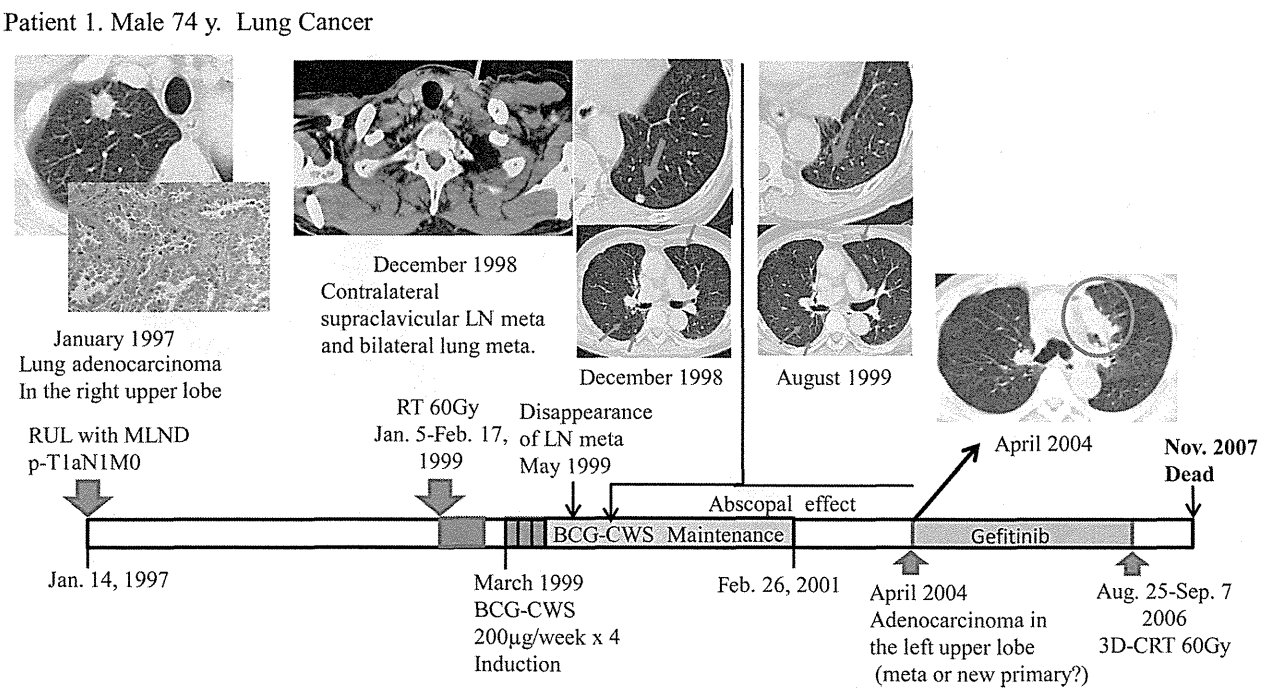

Fig. 1 Clinical course of patient 1. Axial CT images are shown, which are linked to a timeline showing therapy and disease status. *RUL* right upper lobectomy, *MLND* mediastinal lymph node dissection, *LN* lymph node, *RT* radiotherapy, *BCG-CWS* cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin, *3D-CRT* 3-dimensional conformal radiotherapy

this tumor, we performed 3D conformal RT with 60 Gy in 10 fractions in August 2006. Although gamma-knife and whole-brain irradiation were employed for multiple brain metastases, he died due to disease progression in November 2007.

Patient 2

A female patient received a diagnosis of urothelial carcinoma in 1987 at 40 years of age, and initially underwent transurethral resection (TUR) with BCG intravesical therapy. Her clinical course is shown in Fig. 2. She developed lung metastasis and was treated with 2 cycles of chemotherapy consisting of methotrexate, epirubicin, and cisplatin (MEC). Then she underwent basal segmentectomy of the left lung in August 1997, followed by radical cystectomy with an ileal conduit for local recurrence 1 month after the segmentectomy. She remained disease-free until August 2007, when a CT scan showed a new 5-mm pulmonary nodule with a central cavity in the S3 of the right upper lobe of the lung. During observations made up to March 2008, the lesion increased in size to 10 mm in diameter. Therefore, we performed wide wedge resection (WWR) and confirmed the diagnosis of lung metastasis from the urothelial carcinoma. Thereafter, a deep-seated tumor appeared in the same lobe in April 2009. To avoid right upper lobectomy, stereotactic body radiation therapy (SBRT) with 48 Gy in 4 fractions was administered in June 2009 when she was 62 years old. In February 2011, two new lesions with central cavities were detected in the left upper and lower lobes, concomitant with post-irradiation scarring in the right upper lobe.

Because there was no other malignancy except for the left lung metastases, surgery was recommended as a possible treatment after fully discussing the risks and benefits with her surgeon, urologist, and radiologist. However, she refused surgical treatment. Accordingly, informed consent concerning BCG-CWS immunotherapy was obtained. The immunotherapy was started in March 2011 in the same manner as for patient 1. After 10 doses had been administered (November 2011), the two metastases with cavities had completely regressed on CT imaging. The patient has continued on a maintenance dose of BCG-CWS, and she has been disease-free without adverse effects to date (April 2013). Her serum IFN-γ value was <7.8 and 86.6 pg/ml at 1 and 2 months after the start of immunotherapy.

Discussion

The abscopal effect is a rare phenomenon, and the mechanism for it has not been clearly defined. Camphausen et al.

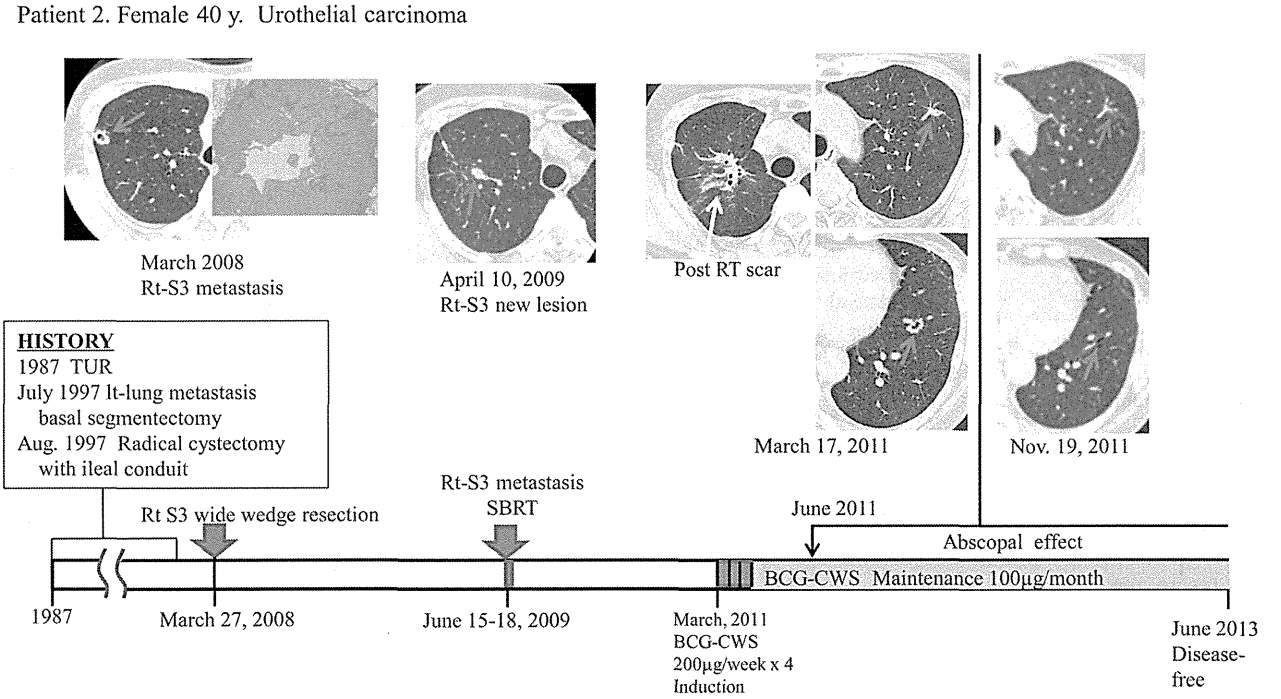

Fig. 2 Clinical course of patient 2. Axial CT images are shown, which are linked to a timeline showing therapy and disease status. The lesions showing an abscopal effect were in the left lung and had central cavities; these lesions presented the same characteristics as the resected and histologically proven metastasis on CT scan. *SBRT* stereotactic body radiation therapy

[15] suggested that the abscopal effect is not tumor-specific but radiation dose dependent. In their animal experiment, they irradiated normal tissue and observed the effects on two types of tumors at a distant site. Their results implicated p53 as a key mediator of the radiation-induced abscopal effect, and suggested that pathways downstream of p53 are important in eliciting this response.

Table 1 summarizes the reports in the literature on abscopal effects observed in clinical studies after RT [2–12]. Clinicians initially attempted to explain the abscopal effect as a radiation-induced increase in the circulating levels of cytokines such as tumor necrosis factor (TNF) [5] or interleukin (IL)-18 [7]. According to a recent clinical report by Postow et al. [12], a patient with NY-ESO-1+ melanoma was treated by local RT and systemic injection of the anti-CTLA antibody ipilimumab, both before and after RT. In this patient, palliative irradiation of a paraspinal thoracic mass led to the regression of distant lesions, in particular a hilar lymphadenopathy of the lung and a splenic lesion. This response was temporarily correlated with signs of an anti-melanoma immune response, namely an increase in NY-ESO-1-specific antibodies, as well as a rise in the frequency of circulating CD4+ T cells expressing the activation marker ICOS, NY-ESO-1-specific interferon gamma-producing CD4+ cells, and HLA-DR-expressing CD14+ monocytes. These data suggest that the abscopal effects of RT are indeed mediated by specific anticancer immune responses.

Recent evidence suggests that local RT can elicit an immune response, and the corresponding effectors (most likely T lymphocytes) then migrate to distant lesions, provoking their regression. RT has the ability to kill cancer cells, and RT-killed cancer cells can be a good source of tumor antigens for inducing cytotoxic T-lymphocyte (CTL) activation. The immune response against other unirradiated malignant cells expressing similar tumor antigens could be augmented. According to an experimental study by Yasuda et al. [16], intratumoral injection of IL-2 not only enhanced shrinkage of the irradiated tumor itself, but also suppressed the development of distant metastasis located outside the RT field, possibly through the induction of a systemic T-cell response. Akutsu et al. [17] reported that a combination of direct intratumoral (i.t.) administration of bone marrow-derived dendritic cells (DCs) and RT in mouse squamous cell carcinoma was able to induce a strong antitumor effect not only against treated local tumors but also against untreated distant tumors. Heat shock protein gp96, also called glucose-regulated protein GRP94, is a stress protein that works as a protein chaperone when DCs take up the antigen via surface molecule CD91 to mediate CTL activation by Toll-like receptors (TLR) 2 and 4. Gp96 is considered a target molecule in explanations of the abscopal effect.

BCG-CWS can activate immature human dendritic cells (iDC), especially bone marrow-derived DC. Although iDC efficiently take up tumor-derived protein/peptides, they barely exhibit antigen presentation or T-cell proliferation. Antigen presentation and T-cell stimulation are enhanced by adjuvants—in this case BCG-CWS, which also induces upregulation of the DC maturation markers CD83 and CD86 and the secretion of inflammatory cytokines such as IL-6, IL-12, and TNF-α. These responses and the increase in antigen-presenting ability, namely cross-presentation, indicate that the activation and maturation of DC is induced by CWS containing mycobacterial peptidoglycan. This suggests that BCG-CWS induces TNF-α secretion from myeloid DC via TLR2 and TLR4, and that the secreted TNF-α induces the maturation of DC [18]. The matured DCs facilitate antigen processing and the loading of tumor-associated antigens into major histocompatibility complex (MHC) class 1 and 2 molecules, which are recognized by CD8 and CD4 T cells, respectively.

Patient 1 remained disease-free at least for 47 months (from August 1999 to June 2003) and then developed left lung adenocarcinoma with brain, lung, and lymph node metastases. No definitive diagnosis as to whether it was a second primary or metastatic lesion was made histologically. However, the new lesion with a tapered bronchus was located in a different place from the lesion that was eliminated through the abscopal effect according to chest CT (Fig. 1).

To date, there has been no description of the time interval between irradiation and the development of the abscopal effect. Postow et al. [12] reported that the abscopal effect was found 4 months after irradiation in a patient with melanoma. In patient 2, two new lesions were detected in the left lung on chest CT about 20 months after SBRT to the right lung metastasis of urothelial carcinoma. Three months after the start of BCG-CWS immunotherapy, the new lesions had completely regressed and this response continued for more than 1 year. How long does immune memory last? Memory T-cell responses were long-lived in the absence of re-exposure to antigens/vaccines/pathogens. Recent studies of anti-smallpox immune memory showed that memory T-cell levels were long-lived but declined with a half-life of 8–15 years [19]. The cross-talk between innate lymphocytes and DC which leads to innate lymphocyte activation and DC maturation is augmented by using a TLR agonist (ligand) such as BCG-CWS. According to a putative mechanism, the booster immunization caused by the administration of BCG-CWS led to a long-term complete response in patient 2.

It is difficult to clearly identify whether the effect was due to BCG-CWS alone, the RT abscopal effect alone, or the RT abscopal effect augmented by BCG-CWS. The targets of pathogen-associated molecular patterns (PAMPs)

Table 1 Radiation abscopal effects observed in clinical studies

Reference	Patient	Tumor type	Treatment	Abscopal effects	Duration of regression	Putative modulator of abscopal effects
Lome et al. [2]	66 years, male	Bladder cancer	RT of primary tumor	10 M following RT, complete regression of lung metastases	23 M	
Krikorian et al. [3]	55 years, female	Malignant lymphoma	RT of eyelid tumor	14 M following RT, complete regression of axillar, abdominal, and parotid adenopathy	51 M following diagnosis	
Rees et al. [4]	49 years, male	Esophageal adenocarcinoma	RT of the primary esophageal lesion	Regression of lung metastases	20 M	
Ohba et al. [5]	76 years, male	HCC	RT of thoracic vertebral bone metastases	10 M following RT, remarkable regression of the primary tumor	35 M	TNF-α
Takaya et al. [6]	69 years, female	Uterine cervical carcinoma	RT of the primary pelvic lesion	6 M following RT, complete regression of para-aortic LN metastasis	NR	
Nakanishi et al. [7]	79 years, male	HCC	RT and TAE of the huge HCC with IVC invasion	5 M following RT, regression of the untreated HCC	NR	Interleukin 18
Formenti et al. [8]		Thymic carcinoma	RT of primary tumor	Complete regression of lung metastasis	38 M	GM-CSF
Isobe et al. [9]		Natural killer cell lymphoma	RT of eyelid tumor	Regression of natural killer cell lymphoma	NR	CD8+ T cells
Lakshmanagowda et al. [10]	65 years, female	Chronic lymphocytic leukemia	RT of massive axillary lymphadenopathy	2 weeks following RT, complete regression of neck lymphadenopathy	6 M	
Okuma et al. [11]	63 years, male	HCC	RT of the mediastinal LN metastasis	Complete regression of lung metastasis	10 years	
Postow et al. [12]	39 years, female	Melanoma	RT of the paraspinal metastasis with ipilimumab	Regression of hilar lymphadenopathy and splenic lesion	11 M	Antibody response to the cancer–testis antigen NY-ESO-1
Our patient 1	74 years, male	Adenocarcinoma of the lung	RT of the supraclavicular LN metastasis followed by BCG-CWS	3 M following RT, complete regression of multiple lung metastasis	47 M	Dendritic cell CTL
Our patient 2	62 years, female	Urothelial carcinoma	RT of the right lung metastasis followed by BCG-CWS	24 M following RT, complete regression of two left lung metastasis	26 M	Dendritic cell CTL

RT radiation therapy, *M* months, *HCC* hepatocellular carcinoma, *NR* not reported, *TNF* tumor necrosis factor, *TAE* transcatheter arterial embolization, *IVC* inferior vena cava, *GM-CSF* granulocyte macrophage-colony stimulating factor, *LN* lymph node, *CTL* cytotoxic T lymphocyte, *BCG-CWS* cell wall skeleton of *Mycobacterium bovis* bacillus Calmette–Guérin

such as BCG-CWS are not lymphocytes but antigen-presenting cells (APC). Currently, BCG-CWS is potentially most effective in patients with minimal disease such as that after resection, after definitive chemoradiation, or after first-line combination chemotherapy. The clinical response obtained in our patients may not have been achieved through BCG-CWS treatment alone without the coexistence of the immunologic cancer antigens that were released by the tumor necrosis caused by RT. On the other hand, the RT-induced cell death causes the release of endogenous danger signals known as damage-associated molecular patterns (DAMP). These DAMPs augment the presentation of tumor antigens released from necrotic tumor cells, ultimately inducing the immune system to attack cancer, thereby mimicking an acute infection. DAMPs and PAMP (BCG-CWS) may share some commonality of expression [20].

According to our phase II study [14], the IFN-γ level does not always elevate after BCG-CWS induction in patients with advanced cancer and/or prolonged chemotherapy. Namely, if the innate immune system is damaged during the patient's clinical course, innate immunity might not be activated by BCG-CWS induction. Thus, we utilized IFN-γ as a marker of innate immune response but not a surrogate marker of the abscopal effect. IFN-γ induction tests were performed during the relatively early phases of BCG-CWS treatment (at the times of the 4th and 5th inoculations). The level of IFN-γ in the peripheral blood was measured before inoculation and 18 h after the inoculation of BCG-CWS. In patients 1 and 2, an elevation of the serum IFN-γ level was observed after BCG-CWS administration. It is worth noting that patient 1 reacted strongly to BCG-CWS; he presented a skin reaction at the inoculation site as well as the swelling of multiple reactive lymph nodes in the neck and axilla. His serum IFN-γ level was also extremely high. Based on these observations, we suppose that BCG-CWS played a more crucial role than DAMPs in his abscopal effect.

Enhancement of the systemic response after local RT in combination with an effective immune adjuvant such as BCG-CWS may provide new insights and suggest new therapeutic avenues to pursue.

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Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Prognostic factors in patients with postoperative brain recurrence from completely resected non-small cell lung cancer

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Keywords
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Abstract

Background: Treatment strategies for brain metastasis from lung cancer have been making progress. The aim of this retrospective analysis was to investigate the post-recurrent prognostic factors in patients with brain metastasis after complete resection of non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed the medical records of 40 patients found to have postoperative brain metastasis from NSCLC in our institution from 2002 to 2008. All patients had undergone radical pulmonary resection for the lung cancer. The impact of numerous variables on survival were assessed, including gender, age, carcinoembryonic antigen (CEA), tumor size, N status, histological type, number of brain metastases, tumor size of brain metastasis, presence of symptoms from the brain tumor(s), and use of perioperative chemotherapy.

Results: The median follow-up was 20.6 months (range, 3.4–66 months). The five-year survival rate from the diagnosis of brain recurrence was 22.5%. In univariate analysis, the favorable prognostic factors after brain recurrence included a normal range of CEA, no extracranial metastasis, no symptoms from the brain metastasis, brain metastasis (less than 2 cm), and radical treatment (craniotomy or stereotactic radiosurgery [SRS]). The multivariate Cox model identified that a small brain metastasis and radical treatment were independent favorable prognostic factors.

Conclusions: This study found that the implementation of radical therapy for metastatic brain tumor(s) when the tumor is still small contributed to an increase in patients' life expectancy.

Introduction

The central nervous system (CNS) is a frequent site of metastasis of non-small cell lung cancer (NSCLC). Brain metastases occur in 30 to 50% of patients with NSCLC, and confer a worse prognosis and quality of life.[1–3] About 50% of stage 3A and 3B NSCLC patients will develop brain metastasis during treatment for lung cancer.[4] Some investigators have reported long-term survival after the resection of a solitary recurrence as brain metastasis.[5–7] The treatment modalities used for metastatic brain tumors, such as stereotactic radiosurgery (SRS), have been improved in recent years.[8] Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), such as erlotinib or gefitinib, have been reported to be an effective treatment for NSCLC patients with brain metastasis and activating mutations in the EGFR gene.[9] Therefore, the role and indications for radical therapy for metastatic brain lesions have remained under discussion.

In this study, to elucidate the prognostic factors for long-term survival of brain metastasis from lung cancer, we reviewed the clinical records of cases treated at our institution.

Patients and methods

This was a retrospective single-center study. It included patients with postoperative brain metastasis as the initial relapse site from surgically resected lung cancer. We reviewed medical records and follow-up data from the Osaka Medical Center for Cancer and Cardiovascular Diseases. Between January 2002 and December 2008, 1091 patients underwent R0-resection and received complete follow-up. Of these

patients, 40 cases (3.6%) with postoperative brain metastasis as initial relapse site were included in this study. The pathological stages of all patients were determined according to the 7th edition of the International Staging System.[10] Standard operations, such as lobectomy or pneumonectomy with complete dissection of the hilar and mediastinal lymph nodes, were performed on all patients.

Follow-up data were obtained by outpatient visits and correspondence with the patients' primary physicians. Our follow-up procedures included physical examinations, chest roentgenography and blood tests, including tests for tumor markers, such as carcinoembryonic antigen (CEA). Chest computed tomography (CT) or 18-fluorodeoxyglucose (FDG) positron emission tomographic (PET) scans were generally performed every six months. In addition, brain CT or magnetic resonance imaging (MRI) was performed annually to detect any brain recurrence. Other metastatic workup also included a bone scan at time of diagnosis to evaluate the patients for bone metastasis.

Postoperative brain recurrence was diagnosed mainly by radiological examination. The histological diagnosis of brain metastasis from NSCLC was confirmed only when we performed craniotomy. In our institution, cranial nerve surgeons determined the operability criteria for brain metastasis. Our inclusion criteria for craniotomy were basically that the tumor location was surgically accessible and we could assure negative surgical margins. After 2004, our indications for SRS were that the tumor size was less than 3 cm, and the number of brain metastases was one to three. In this study, SRS and craniotomy are defined as radical treatments for brain metastasis. Whole brain radiation therapy (WBRT) was performed, not only to prevent recurrence after radical treatments, such as craniotomy or SRS, but also for palliative treatment when the patient could not receive radical treatment for the brain metastasis.

For the analysis of overall survival (OS), each patient's survival time was measured from the date of diagnosis of postoperative brain metastasis until the date of death or the most-recent date of follow-up for surviving patients. We evaluated the following factors: the clinicopathological findings at the time of treatment for the primary lung cancer (type of operation, p-stage, histology, use of adjuvant chemotherapy); and the clinical characteristics at the time of treatment for brain metastasis (gender, age, CEA at the time of brain recurrence, interval to brain metastasis after pulmonary resection, number of brain metastases, tumor size, use of radical therapy, presence of symptoms from the brain tumor, use of an EGFR-TKI, chemotherapy after the treatment for brain metastasis). In this study, we defined the size of the brain metastasis as the size of the biggest brain tumor in the patient if that patient had multiple metastatic brain tumors. On the other hand, if that patient had a single brain metastasis, the size of that tumor was considered to be the size of that metastatic tumor.

Table 1 The clinical and pathological characteristics of the 40 patients with postoperative brain metastasis from non-small cell lung cancer

Gender (male/female)	25/15
Age (years)	65.0 ± 8.9 (49–79)
Primary lesion	
Operation (Lobe/Bil-lobe or Pneumo)	33/7
Pathological stage (1a/1b/2a/2b/3a)	7/6/10/9/8
Histologic classification (Ad/Others)	24/16
Adjuvant chemotherapy (Yes/No)	20/20
Brain lesion	
Interval to brain metastasis after surgery (months)	10.2 ± 8.4 (2.1–32.3)
Number of brain meta (Single/Multiple)	26/14
Tumor size of brain metastasis (mm)	21.5 ± 15.5 (5–70)
Radiotherapy† (Yes/No)	14/26
Radical treatment‡ (Yes/No)	29/11
Symptom before Tx (Yes/No)	26/14
CEA level at the time of recurrence (ng/ml)	1.4–78.6
Extracranial metastasis (Yes/No)	17/23
Chemotherapy after treatment for brain (Yes/No)	12/28
EGFR-TKI (Yes/No)	7/33

†SRS and/or WBRT. ‡2 SRS and/or Craniotomy. Ad, adenocarcinoma; CEA, carcinoembryonic antigen; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors.

Univariate survival analyses were performed using the Kaplan-Meier method, and the differences among the groups were analyzed by the log-rank test. For multivariate analysis, a Cox's proportional hazards regression model was used to evaluate the variables that were significant predictors of survival after the diagnosis of brain recurrence. Univariate and multivariate analyses (SPSS V11.5, Chicago, Illinois) were used to identify the prognostic factors in our population. The Chi-square test was used to compare discrete data. A value of $P < 0.05$ was considered to be statistically significant.

Results

A summary of the 40 patients is shown in Table 1. The study population consisted of 25 men and 15 women. The median age at the time of diagnosis of the brain recurrence was 65 years. At the initial operation, 33 patients underwent lobectomy and seven patients received bilobectomy or pneumonectomy for the primary tumor. Of these patients, seven were classified to have pathological stage 1A, six were in stage 1B, 10 were 2A, nine were 2B, and eight patients were in stage 3A. The histopathological subtype was adenocarcinoma in 24 cases and others in 16 cases. Twenty of these patients received adjuvant chemotherapy after pulmonary resection.

The interval to brain metastasis after surgery ranged from four to 32 months (median: 10 months). Twenty-six patients had solitary brain metastasis and 14 patients had multiple metastatic lesions. The CEA status at the time of recurrence

Table 2 Results of univariate analysis of the prognostic factors for overall survival from the date of postoperative brain recurrence

	Cases	*P*-value	Median Survival (months)
Number of brain metastasis			
Single/Multiple	26/14	0.91	20.4/17.1
EGFR-TKI			
Yes/No	6/34	0.90	26.1/18.7
Interval to brain metastasis from surgery			
>1 year/<1 year	18/22	0.39	21.1/17.4
Adjuvant chemotherapy			
Yes/No	20/20	0.08	26.2/14.2
CEA level at the time of rec			
<5 ng/mL/>5 ng/mL	20/20	0.03	36.3/13.3
Extracranial metastasis			
Yes/No	17/23	0.03	16.6/26.2
Tumor size of brain metastasis			
<2 cm/>2 cm	20/20	<0.01	43.6/13.3
Radical treatment (Craniotomy or SRS)			
Yes/No	29/11	<0.01	27.0/10.8
Symptom from brain metastasis			
Yes/No	26/14	<0.01	17.2/45.4

CEA, carcinoembryonic antigen; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitors; SRS, stereotactic radiosurgery.

ranged from 1.4 to 78.6 ng/mL. Twenty-six patients suffered from neurological symptoms caused by the metastatic brain tumor(s). Of these patients, 23 had only brain metastasis and 17 had brain metastasis with extracranial recurrence. Twenty-nine patients received radical therapy, such as SRS or craniotomy, and 11 patients received WBRT.

In this study, the follow-up period after the time of brain recurrence ranged from 3.4–66 months (median: 20.6 months). The five-year OS rate after the time of recurrence was 22.5%.

Table 2 summarizes the results of the univariate regression model analysis. In this analysis, the favorable prognostic factors after brain recurrence included: a normal range of CEA; no extracranial metastasis; no symptoms from the brain metastasis; small metastatic brain tumor; and radical treatment (craniotomy or SRS). The median OS of patients with a high CEA level was 13.3 months, while that of patients with a normal CEA level was 36.3 months. For the patients with extracranial metastasis, the median OS was 16.6 months, compared with 26.2 months for the patients without extracranial metastasis. The median survival of patients who received radical treatment was 27.0 months compared with 10.8 months for patients who did not receive radical treatment. For the patients with symptoms from the brain metastasis, the median OS was 17.2 months. Statistically significant differences were seen between the two groups in all of these parameters ($P < 0.05$).

Table 3 Results of multivariate analysis of the prognostic factors for overall survival from the date of postoperative brain recurrence

Factor	Odds ratio (95% CI)	*P*-value
CEA level at the time of rec		
<5 ng/mL/>5 ng/mL	0.966 (0.376–2.292)	0.940
Extracranial metastasis		
Yes/No	1.605 (0.786–3.590)	0.181
Symptom from brain metastasis		
Yes/No	2.061 (0.719–5.909)	0.178
Tumor size of brain metastasis		
<2 cm/>2 cm	2.509 (1.023–6.151)	0.041
Radical treatment (Craniotomy or SRS)		
Yes/No	3.619 (1.514–8.652)	<0.01

CEA, carcinoembryonic antigen; CI, confidence interval; SRS, stereotactic radiosurgery.

These five variables showing differences with values of $P < 0.05$ in the univariate analysis were selected for subsequent multivariate analysis (Table 3). The multivariate analysis using Cox's proportional hazards model revealed that a small size of brain metastasis and radical therapy were independent favorable prognostic factors in this patient group ($P = 0.04$, $P = 0.01$). Figure 1 shows the Kaplan-Meier survival plot generated from curves stratified by these factors.

Discussion

The majority of postoperative recurrences of NSCLC are distant metastasis.[11,12] Brain metastases occur frequently as the initial relapse site during the follow-up period after pulmonary resection for NSCLC.[11,13] For lung cancer, some investigators have reported acceptable survival after the resection of distant recurrent lesions, but others have shown

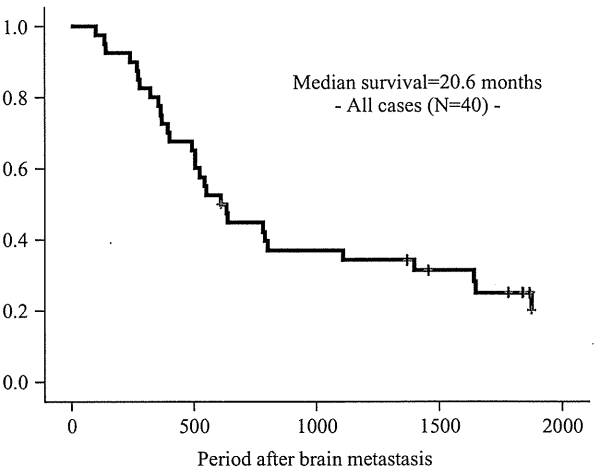

Figure 1 The Kaplan-Meier survival curves for the entire cohort.

data contradicting these conclusions. Abrahams *et al.* demonstrated a satisfactory outcome in patients with brain metastasis, with a median survival time of 18 months and a five-year survival rate of 28.9%.[7] On the contrary, Saitoh *et al.* conducted 24 brain resections, and noted a five-year survival rate of only 8.3%.[5] In this study, the median survival time after recurrence was 20.6 months, and the five-year OS rate after the time of recurrence was 22.5%.

The prognostic factors for survival after the treatment for brain metastasis have not been clarified. In this study, the results of the univariate analyses of the favorable prognostic factors after brain recurrence included normal range of CEA, no extracranial metastasis, no symptoms from the brain metastasis, small metastatic brain tumor, and radical treatment (craniotomy or SRS). The multivariate Cox model identified that a small size of brain metastasis and radical treatment were independent favorable prognostic factors.

Several authors have examined promising prognostic factors in patients with NSCLC who had postoperative brain metastasis. Sakamoto *et al.* reported that local therapy, such as SRS or craniotomy, is one of the significant prognostic factors for NSCLC patients with brain recurrence.[14] In that study, the five-year survival rate after the brain recurrence in patients treated with local therapy was 31.9%, compared to 3.8% for patients without local therapy. In our study, the five-year survival rate of patients treated with local therapy was 31.0%, compared to 0% for patients without local therapy ($P < 0.01$). Based on these results, the patients who receive radical therapy as cerebral local control could be expected to have a longer survival.

To the best of our knowledge, there have been very few reports concerning the relationship between the size of brain metastasis and the prognosis after treatment of brain metastasis. In our study, the median survival of patients whose brain tumor was less than 2 cm was 43.6 months, compared with 13.3 months for patients whose brain tumor was larger than 2 cm. A statistically significant difference was seen between the two groups ($P < 0.05$). The reason for this difference may be that metastatic brain tumors larger than 2 cm are very difficult to control, even when using radical treatment. We found that most of the patients whose brain tumors were larger than 2 cm had intracranial recurrence after treatment for brain metastasis.

By univariate analysis, we also identified that a lack of symptoms from the brain metastasis was a favorable prognostic factor for survival. Aoyama *et al.* showed via multivariate analysis that a good Karnofsky Performance Status (KPS) was a favorable prognostic factor for NSCLC patients with postoperative brain recurrence.[15] In that study, patients with a KPS score of 90 or lower had a 1.69-fold increased risk of death compared with patients with a KPS score of 100. In our report, the five-year survival rate after brain recurrence of patients without symptoms from the brain tumor(s) was 42.8%, compared to 11.5% for patients with symptoms ($P < 0.01$). This difference may be caused by the preservation of the KPS and may be related to the favorable outcome in the patients without symptoms from the brain tumor.

Sakamoto *et al.* reported that the presence of extracranial metastasis at the time of brain recurrence is one of the unfavorable prognostic factors.[14] In our study, a lack of extracranial metastasis at the time of diagnosis for brain metastasis was also a favorable prognostic factor for survival, identified by univariate analysis. However, tumor size of brain metastasis and radical treatment had a greater impact on the patient's survival in our cohort. The patients who had these favorable factors were able to maintain their systemic functions, and as a result, these patients could receive adequate treatment against the extracranial metastasis, including systemic chemotherapy. Therefore, we think that radical treatment for brain tumor(s) might have priority if the patient has brain recurrence with extracranial metastasis.

To date, there have been few prospective studies comparing the survival time after brain metastasis between SRS and craniotomy. Therefore, the evidence based on the current literature is restricted to several retrospective studies, and the results are conflicting. For example, Bindal *et al.* reported that the OS time in patients undergoing resection + WBRT (16.4 months) was statistically longer than that in patients undergoing SRS + WBRT (7.5 months).[16] In contrast, another study revealed a trend toward a longer OS in those receiving SRS + WBRT, but that result did not reach statistical significance.[17] In our cohort, there was no statistically significant difference in the OS time after brain recurrence between the patients who underwent craniotomy and those who underwent SRS (median survival time: 20.4 vs. 26.7 months).

Several authors have recently reported the efficacy of EGFR-TKIs for brain metastasis in NSCLC patients harboring an activating EGFR mutation.[18,19] Park *et al.* revealed that EGFR-TKIs provided high disease control rates, but did not have a significant impact on patient survival. In our cohort, we did not observe any significant difference in the survival time between the patients with and without EGFR mutations (data not shown). However, we did not perform a mutation analysis for all patients because we started the analysis in 2005. Furthermore, the number of patients harboring EGFR mutations was small compared with that of patients without mutations. These factors might have had an impact on the results of the present study. Further accumulation of cases analyzed for mutations will be necessary to perform an adequately powered study of the impact of EGFR mutations and EGFR-TKIs.

Conclusion

In this study, small tumor size of brain metastasis and radical treatment were important favorable predictors for survival in

patients with postoperative brain recurrence. Intracranial recurrence tends to have a greater impact on the patient's systemic activity compared with other sites of recurrence. Therefore, to provide adequate intracranial disease control and to maintain the patient's activities of daily living, it is necessary to detect brain metastases while they are still small during the follow-up period, and patients should undergo radical therapy prior to the development of symptoms from the brain metastasis. To achieve these purposes, the patients' symptoms should be carefully observed, and periodic postoperative follow-up examinations should be performed to detect brain metastases before they become larger than 2 cm.

Disclosure

No authors report any conflict of interest.

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CASE REPORT

Granulocyte-colony stimulating factor (G-CSF) producing malignant pleural mesothelioma: Report of a case

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Abstract

This report presents a case of malignant pleural mesothelioma (MPM) producing granulocyte colony-stimulating factor (G-CSF) that was treated by tumor resection. A 76-year-old male presented with a huge right-side chest wall tumor, along with a slight fever and chest wall pain. Laboratory findings showed an increased white blood cell count (64600 cells/μL) and C-reactive protein level (20.57 mg/dL). The patient underwent surgical removal of the tumor along with tissue from the chest wall and histopathological analysis led to a diagnosis of sarcomatous type of MPM. Immunohistochemical findings for both anti-human G-CSF and interleukin-6 monoclonal antibodies were positive. Although the general condition of the patient quickly improved after surgery, local recurrence occurred two months later and he died of respiratory failure seven months after the operation, though surgery provided symptom relief. G-CSF-producing MPMs usually show a poor prognosis, though less-invasive surgery may be considered for relief of symptoms.

Introduction

Granulocyte colony-stimulating factor (G-CSF) is found in hematopoietic progenitor cells and neutrophil granulocytes, which are generally produced by marrow cells and cells with a hematopoietic origin. Some neoplasms, usually epithelial tumors, also produce G-CSF, while a G-CSF-producing malignant pleural mesothelioma (MPM) is extremely rare, with only six cases reported in English literature. Here, we report a rare case of a G-CSF-producing MPM treated by tumor resection.

Case report

A previously healthy 76-year-old male was admitted for treatment of a huge right-side chest wall tumor. He had a slight fever, and reported chest wall pain and recent weight loss. The patient had been smoking one pack of cigarettes per day for 55 years and worked as an auto mechanic for 60 years, suggesting the possibility of asbestos exposure. Chest computed tomographic (CT) findings revealed a chest wall tumor 11 cm in size that had destroyed the fourth and fifth costal bones, and invaded the lung parenchyma (Fig 1a). A laboratory investigation showed an increased white blood cell (WBC) count of 64600 cells/μL (94.6% neutrophils) and increased C-reactive protein (CRP; 20.57 mg/dL). Major tumor markers in serum were within normal ranges. An 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) revealed increased uptake in the tumor with a maximum standardized uptake value (SUVmax) of 18.7 and diffuse high FDG uptake in bone marrow (Fig 1b). The serum concentration of G-CSF was 71.8 pg/mL (normal range, 5.8–27.5) and that of interleukin (IL)-6 was 40.5 pg/mL (<4.0).

Palliative surgery was planned for the purpose of making a diagnosis and eliminating chest wall pain. The patient underwent surgical removal of the tumor with a portion of the chest wall and partial resection of the right lung. The chest wall defect, 15 cm in size, was reconstructed using a double synthetic woven mesh and latissimus dorsi muscle flap. Histopathological analysis of the resected specimen revealed large diffusely proliferated spindle-shaped cells (Fig 1c). Immunohistochemistry findings showed the tumor to be positive for calretinin, D2-40 (Fig 1d), and epithelial membrane antigen (EMA), and negative for carcinoembryonic

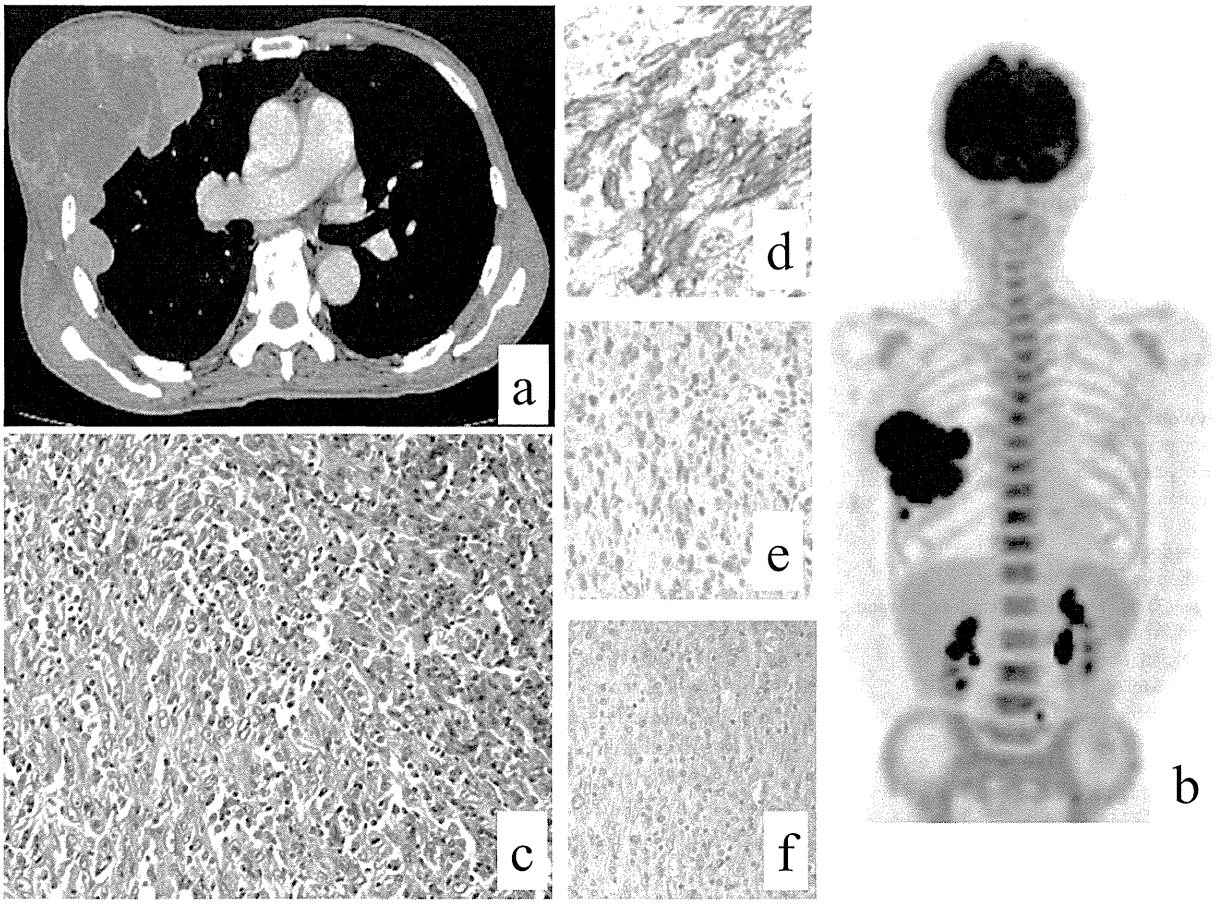

Figure 1 (**a**) Chest computed tomography (CT) image showing a huge mass in the right chest wall that had destroyed the fourth and fifth costal bones, and invaded the lung parenchyma. (**b**) Positron emission tomography (PET)/CT image showed increased uptake in the tumor at 18.7, along with diffuse high fluorodeoxyglucose (FDG) uptake in bone marrow. (**c**) Photomicrograph of the tumor. Large spindle-shaped cells are seen diffusely proliferating. Hematoxylin and eosin (HE), magnification 100×. (**d**) Immunohistochemical analysis for D2-40. The tumor was diagnosed as a malignant pleural mesothelioma. Magnification 100×. (**e**,**f**) Immunohistochemical analysis for anti-human granulocyte colony-stimulating factor (G-CSF) monoclonal antibody (**e**) and anti-human interleukin (IL)-6 monoclonal antibody (f) in the resected specimen were both positive. Magnification 100×.

antigen (CEA) and thyroid transcription factor 1 (TTF-1). These results indicated the tumor was a sarcomatous type of MPM. Immunohistochemical analysis showed that both the anti-human G-CSF monoclonal and anti-human IL-6 monoclonal antibodies were positive (Fig 1e,f). Soon after surgery, the WBC and CRP decreased to a normal level, while the serum concentration of G-CSF also decreased to 8.22 pg/mL. Body temperature also stabilized to within a normal range and the chest wall pain was resolved.

Two months after surgery, chest CT and PET/CT scanning revealed local recurrence in the pleural cavity without distant metastasis. A laboratory investigation showed that WBC, neutrophil, and CRP levels were again increased, while the serum concentration of G-CSF was elevated to 69.0 pg/mL. Concurrent radiotherapy and chemotherapy with cisplatin (CDDP) and pemetrexed (PEM) were immediately planned. Radiotherapy at a dose of 60 Gy was performed, while chemotherapy was discontinued after two courses because of tumor progression. Despite rapid disease progression with the tumor occupying a substantial portion of the right chest cavity, the general condition of our patient remained stable after surgery. Seven months after surgery, he was admitted on an emergency basis for hemoptysis and later died of respiratory failure. The clinical course including diagnosis and treatment is shown in Figure 2.

Discussion

Robinson described the first G-CSF producing tumor in 1974.[1] G-CSF producing malignancies have since been reported in various organs, usually in epithelial tumors. In autopsy study, the most frequent primary sites were the lung

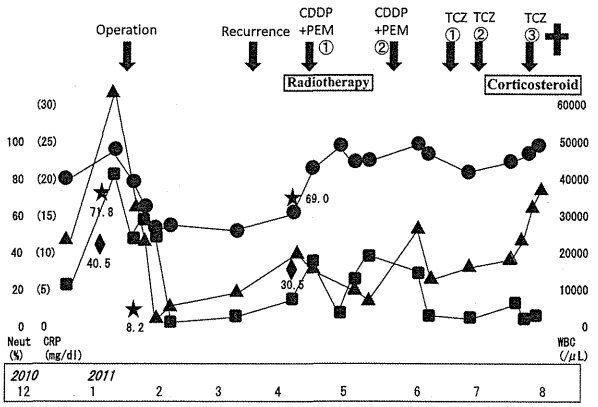

Figure 2 Clinical course including diagnosis and treatment. ■ C-reactive protein (CRP), ▲ White blood cell (WBC) count, ● Neutrophil sequestration, ★ Granulocyte colony-stimulating factor (G-CSF), ◆ interleukin (IL)-6. CDDP: cisplatin, PEM: pemetrexed.

(50%), followed by the liver (7.6%), and stomach (6.0%).[2] The majority are undifferentiated carcinomas.[3] The prognosis of patients with G-CSF producing tumors is usually very poor, regardless of the primary organs; the longest survival period is 14 months.[4,5] There are some possible explanations for the poor prognosis: (i) G-CSF itself has an effect on tumor cell growth; and (ii) G-CSF induces a microenvironment that promotes tumor progression by modulating the tumor stroma.[6]

A G-CSF producing mesothelioma is extremely rare. Only six cases have been reported in English literature (Table 1). All patients were male, with a mean age of 57.6 years (range, 45–76). The most common symptoms were pleural effusion or pleural thickening, such as that seen in common MPM patients, though the proportion of sarcomatous or biphasic histological type was relatively high in G-CSF producing MPM patients.

Four of the seven reported patients, including our case, with a G-CSF-producing MPM received only chemotherapy or supportive care because of advanced stage. Two patients that underwent an extrapleural pneumonectomy (EPP) relapsed soon after surgery and no additional treatment was possible because of their poor general condition. The median survival of the six previously reported G-CSF-producing MPM patients was only 2.7 months after WBC elevation, which was significantly worse than other cases of G-CSF-producing malignancy or common MPM. Our patient received chemoradiotherapy after the initial operation, lived longer than the median term, and showed a generally good condition until just before death. Although novel therapeutic modalities have been recently tested in clinical trials, such as biologic and molecular targeted drug therapies, those treatments are not widely employed. Furthermore, our patient required immediate therapy for the fast growing tumor and

Table 1 Summary of the reported cases of granulocyte colony-stimulating factor (G-CSF) producing malignant pleural mesothelioma

No	Age/Gender	Exposure to asbestos	Symptoms	Max. leukocytes (cells/μL)	Max. neutrophils (cells/μL)	Max. CRP (mg/dL)	Max. Serum G-CSF level (pg/mL)	Histology	Treatment	Survival (weeks)	Reference/Year
1	45/M	Yes	Pleural effusion Pleural thickening	51000	93.0	19.6	50	Por epithelial	Chemotherapy	4	Rikimaru *et al.* 1995[7]
2	48/M	Yes	Pleural effusion Pleural thickening	33100	85.0	Unknown	138	Desmoplastic	Chemotherapy	6/42†	Kasuga *et al.* 2001[8]
3	49/M	Yes	Pleural effusion Pleural thickening	50000	89.0	16.4	130	Biphasic	Surgery	11	Usami *et al.* 2007[9]
4	59/M	Yes	Pleural effusion Pleural thickening	147000	96.2	Unknown	77	Sarcomatous	Surgery	4	Nishimura *et al.* 2006[10]
5	61/M	No	Pleural effusion Pleural thickening	85100	95.0	16.6	67	Mixed	BSC	29	Ohbayashi *et al.* 1999[11]
6	65/M	No	Pleural effusion Pleural thickening Small nodules	53600	93.0	27.1	36	Spindle-cell fibrous	Chemotherapy	28/89†	Yoshimoto *et al.* 2005[12]
7	76/M	Yes	Chest wall tumor	64600	97.8	20.57	71.8	Sarcomatous	Surgery Chemotherapy Radiation	28	Present case 2014

†The anterior is the number of weeks after white blood cell elevation, and the posterior is the number of weeks from the patients first visit. BSC, best supporting care; CRP, C-reactive protein; G-CSF, granulocyte colony-stimulating factor; Por, poorly-differentiated.

relief of severe associated symptoms. We also considered that radiotherapy and chemotherapy were not indicated, as the tumor was quite large and biopsy results did not lead to a diagnosis.

Some malignant tumors including MPM secrete IL-6, a multifunctional cytokine[13] that may play a crucial role in resistance to chemotherapy or hormonal therapy,[14] as it might be involved in angiogenesis via expression of vascular endothelial growth factor (VEGF), promote establishment of metastatic tumors,[15] and cause cachexia.[16]

In the present case, both G-CSF and IL-6 were elevated, and the trend of fluctuation was in line with disease progression. Interestingly, there may be a relationship between G-CSF and IL-6, as Shannon *et al.* reported that IL-6 might be a promoter of G-CSF.[17] Meanwhile, G-CSF may induce IL-6 production because it stimulates the production of cytokines. Therefore, tumor growth might be accelerated by the interaction of these cytokines, in addition to their individual actions. Inhibition of the functions of these cytokines may contribute to effective treatment for G-CSF-producing MPM. Furthermore, Tachibana *et al.* reported that the anti-G-CSF antibody inhibited cultured cells from a transitional cell carcinoma of the bladder that had been stimulated by G-CSF.[18] Recently, two new drugs were developed to inhibit IL-6 activity,[19,20] which may improve treatment options for G-CSF- or IL-6-producing malignancies, though further studies are needed.

Conclusion

We encountered a rare case of a G-CSF-producing MPM that was treated by a tumorectomy. The patient had early recurrence and died seven months after surgery, demonstrating the degree of malignancy of such a neoplasm. Interestingly, the general condition of our patient was stable for a relatively long period after the operation. Although novel therapeutic modalities are currently being tested and encouraging results are expected, less-invasive surgery may be considered to both prolong survival and maintain patient quality of life, depending on prognosis.

Disclosure

No authors report any conflict of interest.

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