sorafenib is necessary. We are presently undertaking a prospective molecular translational study (2010-2012) in a cohort of Japanese patients with sorafenib-treated HCC.

Multiple lung metastases were frequently observed among responders to sorafenib (38%) but were less common among nonresponders (5%). Based on a Japanese follow-up survey of patients with primary HCC, lung metastasis was observed in 7% (169/2355) of the patients at the time of autopsy.[20] Another study demonstrated that 15% of patients were found to have extrahepatic metastases, and lung metastasis was detected in 6% of 995 consecutive HCC patients.[21] When compared with these data from large-scale studies, the frequency of lung metastasis among responders to sorafenib seems quite high. In addition, a poorly differentiated histological type tended to be more common among responders, although the correlation was not significant.

In conclusion, we found that *FGF3/FGF4* gene amplification, multiple lung metastases, and a poorly differentiated histological type may be involved in the response to sorafenib.

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Pilot Study of Duloxetine for Cancer Patients with Neuropathic Pain Non-responsive to Pregabalin

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Abstract. *Background: Neuropathic pain frequently occurs in cancer patients, but no drug therapy has been established for this type of disorder. The purpose of this study was to investigate the effect of duloxetine in cancer patients suffering from neuropathic pain. Patients and Methods: The subjects of the study were 15 cancer patients with neuropathic pain who visited the Kinki University Faculty of Medicine Hospital and met the International Association for the Study of Pain diagnostic criteria for neuropathic pain. Duloxetine was administered to patients in whom pregabalin could not be administered. The influence of duloxetine was investigated retrospectively with the use of a numerical rating scale. Results: Pain was reduced in 7 out of the 15 patients. Sleepiness and the light-headed feeling were improved in four patients, in whom, however, the pain was not reduced. Thus, duloxetine was judged to be effective in 11 patients. The maintenance dose of duloxetine was 20-40 mg/day. Conclusion: Duloxetine administration may be effective for neuropathic pain in cancer patients who cannot tolerate pregabalin administration.*

Cancer patients may experience pain from diverse sources, including chemotherapy-induced neuropathic pain (NP), pain after thoracotomy or mastectomy, and pain associated with a bone tumor or with spinal cord invasion (1). The incidence is high and 33% of patients suffering from cancer pain have NP (2). Thus, treatment of NP is important, but the underlying mechanisms are not well understood and no specific drug therapy has been established. The drugs used for the treatment of NP in cancer are currently selected based on evidence of their efficacy for non-cancer pain.

Various drugs are useful for the treatment of NP (3), for this reason opioids, tricyclic antidepressants (TCAs), gabapentin, and pregabalin are often used (4). Randomized controlled trials (RCTs) have shown that opioids (particularly, oxycodone) are effective for NP in cancer patients (5) but some patients are reluctant to use opioids (6). TCAs are also effective for NP (7) but cause adverse effects such as dry mouth, sleepiness, constipation and a light-headed feeling (8). Furthermore, it may not be possible to reduce the opioid dose in combination with TCA treatment for NP in cancer patients (9). Similarly, gabapentin is effective for NP, but also causes adverse effects of withdrawal symptoms, a light-headed feeling, sleepiness, edema, and gait disturbance in 66% of patients (10).

Pregabalin has a marked effect on pain (11) that allows morphine dosing to be significantly reduced in combination therapy compared to other drugs for NP (12). Thus, pregabalin is frequently used as the first choice for treatment of NP and has been shown to have a particular effect in patients with pancreatic cancer treated with oxaliplatin (13). Treatment with 150 mg/day pregabalin for 2-6 weeks improved neuropathy, after oxaliplatin administration, from grade 2-3 to grade 1-2 in 11 out of 23 patients with digestive organ cancer (14). NP was improved or maintained at the same level by pregabalin in about 70% of the patients, there was no effect in 17% and the administration was discontinued in 13% of patients. However, 57% of the patients complained of a light-headed feeling. These results suggest that new drugs with fewer adverse effects are required for the treatment of NP in cancer patients.

Duloxetine is an antidepressant serotonin-noradrenaline reuptake inhibitor that is also indicated for diabetic NP and fibromyalgia (15, 16). Along with pregabalin, gabapentin and TCAs, duloxetine is recommended as a first choice in the Neuropathic Pain Special Interest Group Guidelines (17).

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Table I. *Clinical characteristics of the patients.*

Patient	Age (years)	Gender	PS	Cancer type	Cause of pain	Analgesic (NSAIDs)	Opioid	Pregabalin (mg)	Adverse effect
1	71	M	1	Unknown	PTX	No	No	150	Light-headed feeling
2	52	M	2	CRC	FOLFOX	Yes	Sustained release oxycodone, 30 mg	300	Sleepiness
3	57	M	2	CRC	XELOX	Yes	Sustained release oxycodone, 60 mg	300	Sleepiness
4	31	M	1	CRC	FOLFOX	Yes	Sustained release oxycodone, 75 mg	No	Sleepiness
5	76	M	1	Lung	PTX	Yes	No	No	Sleepiness, light-headed feeling
6	69	F	2	Breast	Spinal cord invasion	Yes	Sustained release morphine, 30 mg	No	Light-headed feeling
7	68	M	1	CRC	XELOX	No	No	150	Sleepiness
8	72	M	3	Lung	Spinal cord invasion	Yes	Sustained release oxycodone, 640 mg	No	Sleepiness
9	79	M	3	Lung	Spinal cord invasion	Yes	Sustained release oxycodone, 30 mg	225	Light-headed feeling
10	44	F	1	Breast	PTX	No	No	125	Sleepiness, edema
11	61	F	1	Breast	PMPS	No	No	150	Light-headed feeling
12	75		1	CRC	Spinal cord invasion	Yes	Transdermal fentanyl, 1 mg	No	Light-headed feeling
13	40	F	1	Breast	PTX	No	No	150	Sleepiness
14	59	M	1	CRC	Spinal cord invasion	Yes	No	No	Sleepiness
15	68	F	1	Breast	NabPTX	No	No	150	Light-headed feeling

CRC, Colorectal cancer; PS, performance status; FOLFOX, leucovorin + 5-fluorouracil + oxaliplatin; XELOX, capecitabine + oxaliplatin; PTX, paclitaxel; NabPTX, abraxane; PMPS, postmastectomy pain syndrome; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

The efficacy of duloxetine for diabetic NP and fibromyalgia has been widely investigated, but few studies have been performed for cancer patients, with only one report on the effect of duloxetine on chemotherapy-induced peripheral neuropathy (18). Therefore, the objective of this study was to investigate the effect of duloxetine in cancer patients with NP in whom pregabalin treatment was unsuccessful.

Patients and Methods

This study was performed at the Kinki University Faculty of Medicine Hospital, in Osaka, Japan. We retrospectively analyzed 15 cancer patients (9 males and 6 females). The subjects of this study were cancer patients who visited the Kinki University Faculty of Medicine Hospital between April 2011 and October 2011 and met the International Association for the Study of Pain (IASP) diagnostic criteria for NP (19).

None of the patients had major frequent causes of NP not related to cancer, such as diabetes or microangiopathy. Two psycho-oncologists performed diagnosis for mental disorders, and no patients met the criteria (20) for depression and anxiety disorder.

Opioids were administered to the patients who suffered from excruciatingly severe pain the opioid treatment, but some patients did not receive opioids because they only suffered from chemotherapy-induced peripheral neuropathy and did not wish to take them. The first 15 cancer patients were diagnosed with NP by the IASP diagnostic criteria for NP. The patients were treated with duloxetine because pregabalin could not be administered, was ineffective, or was effective but the dose could not be elevated due to adverse effects. Pregabalin had been discontinued in these patients: nine patients had sleepiness, seven had an unpleasant light-headed feeling and one patient had edema. Two out of the 15 patients had two adverse effects of pregabalin.

The patients met the following inclusion criteria: diagnosis of cancer with NP, age ≥18 years, and no history of depression based on an interview and a self-completed questionnaire. The flow chart for the grading of NP specified by the IASP was used to diagnose neuropathic pain (19).

Duloxetine administration was initiated after breakfast from 20 mg/day. A numerical rating scale (NRS) was evaluated 3-7 days after initiation to evaluate changes in symptoms, adverse effects, and compliance. Treatment was continued when the pain was reduced (≥33% reduction from baseline on the NRS) after duloxetine administration at 20 mg/day for 3-7 days. When the pain was not reduced, the dose was increased to 40 mg/day and a re-evaluation was performed after one week. Administration was continued when adverse effects, such as sleepiness, were improved, even though pain was not reduced. When adverse effects were unchanged or worsened, duloxetine was discontinued and the treatment was changed. In the earlier treatment with pregabalin, the drug was discontinued or the dose was reduced when adverse effects were severe. Duloxetine was administered concomitantly with pregabalin when adverse effects were tolerable but the effect was insufficient.

An analgesic effect of duloxetine has been reported at one week after initiation of administration for diabetic NP (21). However, we thought that a longitudinal assessment over a far longer period

Table II. *Effect of duloxetine in cancer patients with neuropathic pain.*

Patient	Duloxetine (mg)	NRS			Effect
		Before administration	1 Week after administration	2-4 Weeks after administration	
1	20	5	2	2	Yes
2	20	5	5	4	Improvement of sleepiness
3	20	4	4	4	Improvement of sleepiness
4	20	5	3	3	Improvement of sleepiness
5	20	8	8	9	No
6	20	7	3	2	Yes
7	40	7	4	2	Yes
8	40	4	3	3	No
9	20	7	3	3	Yes
10	20	8	5	4	Yes
11	20	8	5	4	Yes
12	20	10	5	3	Yes
13	40	5	8	9	No
14	40	5	7	7	No
15	40	5	5	5	Improvement of light-headed feeling

NRS, Numerical Rating Scale.

should be performed. Therefore, we evaluated the scale at one week after administration and two to four weeks after administration. Duloxetine was classified as 'effective' in patients in whom it was administered for ≥4 weeks, and 'ineffective' in those at whom the drug was discontinued within four weeks. Concomitant treatment with analgesics, such as opioids and other adjuvant analgesics was not changed throughout the study period.

Results

Clinical characteristics of the 15 patients are presented in Table I, including Eastern Cooperative Oncology Group Performance Status (PS) on the first day of duloxetine administration and of the use of concomitant opioids and NSAIDs. Pain was reduced in 7 out of the 15 patients and sleepiness and a light-headed feeling were improved in four patients in whom pain was not reduced. Thus, duloxetine was judged to be 'effective' in 11 patients (Table II). In the remaining four patients, no effect on pain was observed in three cases, and duloxetine was discontinued at 2 weeks because there was also no improvement of adverse effects. In the other case, continuation of duloxetine was difficult due to decrease in PS. Adverse effects of duloxetine included digestive symptoms, such as nausea, but the effects were mild and did not prevent administration to any patient. The maintenance dose of duloxetine was 20-40 mg/day in patients who received duloxetine for ≥2 weeks.

Discussion

The pain was reduced in 7 out of the 15 patients and the adverse effects were improved in four patients, indicating that duloxetine was effective in 11 patients. NP caused by peripheral neuropathy as an adverse effect of anticancer drugs requires treatment since it impairs the quality of life (QOL) of patients and may lead to suspension or discontinuation of the anticancer treatment. However, NP may often be overlooked, since attending physicians has been found to diagnose diabetic neuropathy (benign disease-associated NP) in only half of the patients (22). Moreover, pain in cancer patients is likely to be underestimated, with a lower estimation of pain reported in about 50% of patients (23). In addition, in a study performed on lung cancer patients, fewer than 30% of them were able to explain their concerns to their physician (24). The pathological condition may be aggravated when anticancer treatment is continued in cases in which physicians underestimate NP caused as adverse effects of anticancer drugs and patients cannot convince the physician of the severity of the pain.

It has also been reported that 40% of cancer patients are in a depressive state that requires treatment (25) and that this depression may influence the rejection of the anticancer therapy (26). Therefore, treatment of depression is necessary, but this condition is difficult to be evaluated and is frequently overlooked by both physicians and nurses (27, 28). One reason is the marked overlap of cancer symptoms with the diagnostic criteria for depression, with physicians, nurses, and patients considering that "distress is natural because of cancer". Psychomotor inhibition is a characteristic of depression, in which patients cannot organize their thinking and feel too distressed to talk (29). This may lead to a delay in treatment of NP and more attention should be attributed to this issue.

Pregabalin is frequently used as a first choice drug for NP, but causes diverse adverse effects including somnolence, a light-headed feeling and edema (30). In addition, insomnia,

nausea, headache, and diarrhea have been reported as withdrawal symptoms (31). Suicidal ideation may also be induced by novel antiepileptics, with the risk of self-injurious behavior found to be increased three-fold by depressive state-inducing antiepileptics, although pregabalin has not been found to increase this risk (32). In contrast, the Health News Letter of Canada reported 16 cases of suicidal ideation and one suicide attempt in patients receiving pregabalin (33). Thus, careful administration of pregabalin is necessary, although the drug is effective for pain. Selection of an adjuvant analgesic requires consideration of adverse effects, in addition to the effect on pain, and an appropriate drug should be used for individual patients.

In a meta-analysis, Quilici *et al.* found that the efficacy of once-a-day duloxetine administration for diabetic NP was equivalent to those of pregabalin and gabapentin (34). In a RCT, Tanenberg *et al.* showed the non inferiority of 60 mg/day duloxetine compared to 300 mg/day pregabalin for diabetic NP in patients for whom gabapentin was ineffective (35). The study reported high incidences of nausea, anorexia, and insomnia in the duloxetine group and of edema in the pregabalin group. In 39 colorectal cancer patients with NP following oxaliplatin treatment, Yang *et al.* found that 30-60 mg/day duloxetine improved the score on a visual analog scale in 19 out of 30 patients in whom duloxetine could be continued (18). In our study, duloxetine was administered at a lower dose of 20-40 mg/day, which facilitated the continuation of administration while preventing pain aggravation. Mittal *et al.* showed that duloxetine has been suggested to have less effect on NP compared to pregabalin (36), while having a higher withdrawal rate due to adverse effects; however, this study was performed in non-cancer patients with diabetic NP. Duloxetine is reported to frequently cause nausea, but the incidence of adverse effects that are frequently induced by pregabalin, including edema, sleepiness, and a light-headed feeling, was low. Furthermore, duloxetine only requires administration once a day. These properties suggest that duloxetine may be a useful alternative treatment for patients to whom pregabalin cannot be readily administered.

There are several limitations of this study. Firstly, duloxetine may not have acted only on NP. About 40% of cancer patients have depression that requires treatment; the pain threshold decreases and the sensitivity to pain increases in patients in a depressive state (37). Since there are many uneasy and depressive patients among cancer patients, even if they do not meet the DSM-IV-TR criteria for diagnosis of depression and anxiety disorder, duloxetine may well be effective psychologically. In our study, no patients met the DSM-IV-TR criteria for diagnosis of depression, but it cannot be ruled out that the pain could have been reduced through elevation of the pain threshold due to an improvement in depression. There is a possibility that duloxetine was effective in both activation of the descending pain modulatory system and the improvement of depressive mood which does not meet the DSM-IV-TR criteria for diagnosis. Secondly, patients who could be readily investigated retrospectively were selected as subjects and the study was performed at a single hospital. This makes it difficult to generalize the results to other facilities. Moreover, the duration of illness, existant concomitant diseases, concomitant use of NSAIDs, drugs other than adjuvant analgesics, and the psychosocial background, such as the educational level and the employment, were not surveyed. Further studies are necessary in order to establish the effects of these factors.

Within these limitations, the results of this study suggest that duloxetine could reduce the NP and the adverse effects in cancer patients. This is also the first study to report the use of duloxetine for cases in which pregabalin could not be used. The effect may have partly taken place due to elevation of the pain threshold through the antidepressant effect of duloxetine. However, this may still be useful since many antidepressants cannot be readily administered to cancer patients and the depressive state of cancer patients is currently underestimated and often untreated (26, 27, 38).

Our results show that duloxetine may be useful for NP in cancer patients who cannot tolerate administration of pregabalin.

Conflicts of Interest

Authors report no declarations of interest.

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<Original>

The health impact of intimate partner violence on adult female patients and the role of psychosomatic medicine in Japan

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Summary Objectives : The primary aim of this study was to explore the health impact of intimate partner violence (IPV) on the physical and psychological condition of adult patients, and to clarify the pathology of IPV. The secondary aim was to clarify the role of psychosomatic medicine (PSM) doctors in IPV survivor treatment and clinical practice.

Methods : We conducted a study with IPV survivors over 20 years old among patients whose first visit to our department was between January 2004 and December 2010. All patients were asked a wide range of health questions and explained their experiences of abuse. We conducted semi-structured interviews and examined their Self-rating Depression Scale (SDS) and State-Trait Anxiety Inventory (STAI) scores.

Results : Survivors of IPV suffered various acute and chronic physical health problems and frequent mental distress such as depressive mood and anxiety. Patients sometimes complained of vague and incomprehensible symptoms. The four factors (physical, psychological, sexual, economical/social aspects) of IPV are often combined.

Conclusions : The pathology of IPV is based on a power structure and often contains generational links and reproduction of violence. PSM doctors play an important role for IPV survivors through early intervention and coordination with multiple facilities.

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Key words : Intimate partner violence, Psychosomatic medicine, Women's health, Generational links, Reproduction of violence

Introduction

Intimate partner violence (IPV) is a serious human rights abuse and public health issue, which leads to substantial physical and mental health consequences[1)~4)]. All types of IPV (physical, sexual and psychological violence) have immediate and long-term effects on health[5)6)]. IPV is also related to increased medical costs[7)]. Physically and/or sexually abused women are nearly three times as likely to report fair or poor health and their indicators are linked to hospitalization risk and annual doctor visit rates[8)]. Such aspects signify that IPV is not only a personal problem but a public issue as well. The total care of these abused patients, therefore, should be a primary concern to health care professionals.

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IPV is a prevalent problem in every country[9)~13)] and an effort to reduce IPV has been made all over the world. In Japan, the Law Relating to Prevention of Spousal Violence and the Protection of Victims was enacted in 2001 and amended in 2004 and 2007[14)]. However, Japanese society does not have a long history of recognizing IPV and there is still a lack of information and awareness among health care professionals, as well as citizens. This unfamiliarity may come from the Japanese cultural background where people consider IPV to be a private matter between partners. It is necessary to start with revealing and verifying the current status of IPV survivor cases in medical fields in Japan. Health care professionals should understand the complex issues involved in IPV and should be capable of assessing the physical and mental health condition of IPV survivors.

Psychosomatic medicine (PSM) was officially established in Japan in 1996 as a specific field in which "psychosomatic disorders" are dealt with, independent from psychiatry. PSM doctors, who deal with stress-related physical symptoms and psychological distress, have been increasingly taking care of IPV survivors that have various combined physical and psychological symptoms.

The primary aim of this study was to explore the health impact of IPV on the physical and psychological condition of adult patients, and to clarify the pathology of IPV. The secondary aim was to clarify the role of PSM doctors in IPV survivor treatment and clinical practice. Three illustrative cases are presented and a structured analysis has been conducted to reveal the difficulties of IPV survivors.

Materials and Methods

1) Design and setting

This study was conducted to screen for IPV survivors among the patients whose first visit to the Department of Psychosomatic Medicine, Sakai Hospital, Kinki University Faculty of Medicine was between January 2004 and December 2010. Eligible patients were over 20 years of age. Our department is classified as part of internal medicine and deals with patients complaining of physical symptoms due to psychosocial distress. Approximately 600 new patients visit our department per year and female/male patient ratio is about 2.5 : 1.

All new patients were asked to fill in questionnaires upon their first visit to our department. The questionnaires asked a wide range of health questions including their age, sex, educational background, employment status, marital status and family composition, symptoms and medical history. After that, patients were asked directly by doctors about their experiences of abuse in the past and the present. Semi-structured interviews were then conducted with patients who had the possibility of being IPV survivors and agreed to participate in this study. The participants were restricted to patients who were aware of their experiences of abuse and were willing to talk about them. Cases with a history of psychiatric disease and subject to a lawsuit were excluded in order to avoid biased comments and improve reliability. The interviews contained questions about past and present experiences of abuse by their intimate partners and family members, what types of violence they were subjected to, the correlation between their symptoms and IPV, and the tendency of violence by patients themselves.

2) Psychological measurement

The Self-rating Depression Scale (SDS)[15)] and the State-Trait Anxiety Inventory (STAI)[16)] were used to evaluate emotional distress in terms of depression and anxiety. In SDS, a cut-off score of 50 was adopted in this study to determine that patients were considered to be in a depressive state. In STAI, cut-off scores of 42/45 (STAI-S/T

Table 1 Concept of IPV

Physical abuse
Beating
Kicking
Using a weapon against partner
Choking
Burning partner with cigarettes
Psychological/Emotional abuse
Verbal attacks
Ignoring partner
Threatening
to commit suicide
to throw partner out
Sexual abuse
Forcing sexual intercourse violently
Sabotaging contraceptive efforts
Economical/Social abuse
Refusing to support family financially
Stealing money
Forbidding partner from working
Threatening partner with financial blockage
Overseeing and restricting a partner's behavior
Controlling what partner does
who partner sees
where partner goes
Treating partner like a servant

for female) and 41/44 (STAI-S/T for male) were adopted to determine that patients were considered to have a tendency towards anxiety.

3) Diagnosis

In this study, each patient's mental status was evaluated via a formal medical interview, leading to a diagnosis using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[17]. Physical diseases such as irritable bowel syndrome, headache and asthma were diagnosed as psychosomatic disorders based on "A guideline for the diagnosis and treatment of psychosomatic disorders 2006"[18]. Sleep apnea syndrome was diagnosed based on the criteria of American Academy of Sleep Medicine, and hypertension was diagnosed based on the criteria of the World Health Organization (WHO).

4) The concept of IPV

IPV contains multiple factors and is classified mainly by physical and psychological aspects[19]. We defined four aspects of IPV as follows : physical abuse (for example beating, kicking, using a weapon and/or burning partner with cigarettes), psychological/emotional abuse (abusing a partner verbally or ignoring/threatening them), sexual abuse (forcing unwanted sexual intercourse and/or refusing to use contraception), and economical/social abuse (threatening a partner with financial blockage, stealing money, restricting a partner's behavior). We selected the IPV elements of isolation and using male privilege, such as controlling who a partner sees or where a partner goes and treating a partner like a servant, and placed them under a 4th heading of "economical/social abuse"[20]. Details are listed in Table 1.

5) Ethical assessment

This study was conducted according to the ethics rules of our hospital. The purpose of this study was explained to the patients and informed consent was obtained for publication of study. Written consent was further acquired from the three patients involved in the cases featured in this paper.

Results

Demographic and Clinical Characteristics

Eighty-seven patients revealed their history of abuse, from their childhood to ongoing experiences. Seventeen patients, who had a history of psychiatric disease or were subject to a lawsuit, were excluded from this study. Seventy out of the eighty-seven cases where patients clearly realized the correlation between their symptoms and IPV experiences were chosen for this study. There was only one male patient. Detailed demographic characteristics of the patients are listed in Table 2.

The patients ranged in age from in their twen-

Table 2 Characteristics of patients

Clinical Characteristics	N	(%)
Total patients	70	100
Age (mean ± SD), years	47.1 ± 15.5	
range	20-70	
Sex		
Female	69	98.6
Male	1	1.4
Education		
9 years and less	9	12.9
9-12 years	34	48.6
more than 12 years	27	38.6
Employment		
Full-time	9	12.9
Part-time	8	11.4
Unemployed	51	72.9
Student	2	2.9
Marital Status		
Single/Dating	11	15.7
Married/Cohabitating	41	58.6
Divorced/Separated	16	22.9
Widowed	2	2.9
Experience of abuse in their childhood	15	21.4
Own tendency to violence	6	8.6

SD = Standard deviation
% may not sum to 100 due to rounding

Table 3 Presented symptoms

Present symptoms	N	(%)
Physical symptoms		
Fatigue	30	42.9
Insomnia	27	38.6
Feeling of difficulty breathing	24	34.3
Pain (including headaches)	23	32.9
Appetite loss/body weight loss	20	28.6
Palpitations	16	22.9
Dizziness/faintness	8	11.4
Nausea/vomiting	7	10.0
Diarrhea/constipation	5	7.1
Injuries	5	7.1
Numbness	5	7.1
Tinnitus	5	7.1
Urinary problems	3	4.3
Urticaria	2	2.9
Others	8	11.4
Psychological/Emotional symptoms		
Anxiety	35	50.0
Depressive mood	32	45.7
Irritation	18	25.7
Helplessness/powerlessness	15	21.4
Fear	12	17.1
Apathy	11	15.7
Loss of self-esteem	11	15.7
Difficulty focusing	10	14.3
Flashbacks	10	14.3
Feelings of worthlessness	9	12.9
Guilt	9	12.9
Self-blame	9	12.9
Shame, embarrassment	8	11.4
Over-eating	7	10.0
Panic attacks	6	8.6
Anger	5	7.1
Confusion	5	7.1
Suicidal ideation	5	7.1
Others	23	32.9

* Multiple answers given

ties to in their seventies and average age was 47.1 ± 15.5 years old. In Japan, compulsory education is comprised of 6 years in elementary school and 3 years in junior high school. After completing compulsory education, a child may go on to high school for 3 years and then further education, such as college/university or postgraduate college. Fifty-one patients (72.9%) were unemployed (housewives were included in this definition). Fifteen out of seventy (21.4%) patients had an experience of being battered, including sexual violence, by their parents or brothers in their childhood. Six patients (8.6%) revealed their own tendency to violence toward their children.

Symptoms present in the patients are listed in Table 3. Various physical symptoms such as fatigue, insomnia, feeling of difficulty breathing, pains, appetite/body weight loss, palpitations, dizziness/faintness, nausea/vomiting, diarrhea/constipation, injuries and others were associated with IPV cases. At the same time, battered patients were likely to present psychological complaints such as anxiety, depressive mood, irritation, a sense of helplessness, fear, apathy, loss of self-esteem and suicidal ideation. The characteristics of their symptoms or complaints were vague

Table 4 Physical (psychosomatic) disease and psychiatric diagnosis

Diagnosis	N	(%)
Physical (psychosomatic) disease diagnosis		
Injuries (bruises, burns, bone fractures)	5	7.1
Tension headache/Migrane	10	14.3
Asthma	5	7.1
Sleep apnea syndrome	3	4.3
Hyperventilation syndrome	11	15.7
Hypertension	12	17.1
Irritable bowel syndrome	5	7.1
Chronic pain syndrome	5	7.1
Urticaria	2	2.9
Premenstrural syndrome	1	1.4
Others	4	5.7
None	7	10.0
Psychiatric diagnosis		
Major depressive disorder	13	18.6
Anxiety disorders	18	25.7
Panic disorder	6	8.6
Social anxiety disorder	3	4.3
Obsessive-compulsive disorder	2	2.9
Posttraumatic stress disorder	3	4.3
Generalized anxiety disorder	4	5.7
Eating disorders	5	7.1
Anorexia nervosa	0	0
Bulimia nervosa	5	7.1
Adjustment disorders	25	35.7
With depresive mood	7	10.0
With anxiety	5	7.1
Mixed anxiety and depressive mood	11	15.7
Mixed disturbance of emotions and conduct	1	1.4
Unspecified	1	1.4
Personality disorders	3	4.3
Other psychotic disorders	4	5.7
None	2	2.9

and varied, and sometimes seemed incomprehensible and unrelated psychosomatic manifestations. Chief complaints changed as time passed. The reason for their medical visit was sometimes unclear and inconsistent, for example, some explained the cause of their injury as an accident but this often seemed unlikely. Some patients were frightened by or rejected medical staff of the opposite sex.

Both the physical (psychosomatic) disease diagnosis and psychiatric diagnosis are shown in Table 4.

Patients suffered various acute and chronic health problems of physical manifestations such as injuries (bruises, burns and bone fractures), headaches, asthma, sleep apnea syndrome, hyperventilation syndrome, hypertension, irritable bowel syndrome and others. In addition, many of them were in a depressive and anxiety state. The SDS scores of 70 patients were 55.8 ± 9.7 and 42 patients had higher scores than cut-off scores of 50. The STAI-S/T scores of 69 female patients were 54.1 ± 13.5/56.4 ± 13.2. 46 female patients had higher scores than cut-off scores of 42/45 for females and the sole male patient had a higher score than cut-off scores of 41/44 for males. Adjustment disorders were 35.7% and the subtypes were determined by reference to SDS/STAI scores and patients' symptoms. Major depressive disorder was 18.6%, anxiety disorders including panic disorders were 25.7%, bulimia nervosa was 7.1% and others, including personality disorders, were 10.0%.

The four factors (physical, psychological, sexual, economical/social aspects) of IPV are often combined. The results are shown in Figure 1.

Case reports

Three illustrative cases were presented.

Case No. 1 contains typical characteristics of IPV survivors. A 41-year-old female complained of anxiety, appetite loss, insomnia, depressive mood, nausea and epigastralgia. She had not experienced any abuse from her parents. She had struggled with physical and psychological violence by her husband and divorced him once. He apologized to her, swore that he would never be violent again and begged her to restore the relationship. She agreed to remarry him, however he began to kick and hit her again. She was abused physically, verbally, threatened with financial blockage and sexually assaulted. Gradually she

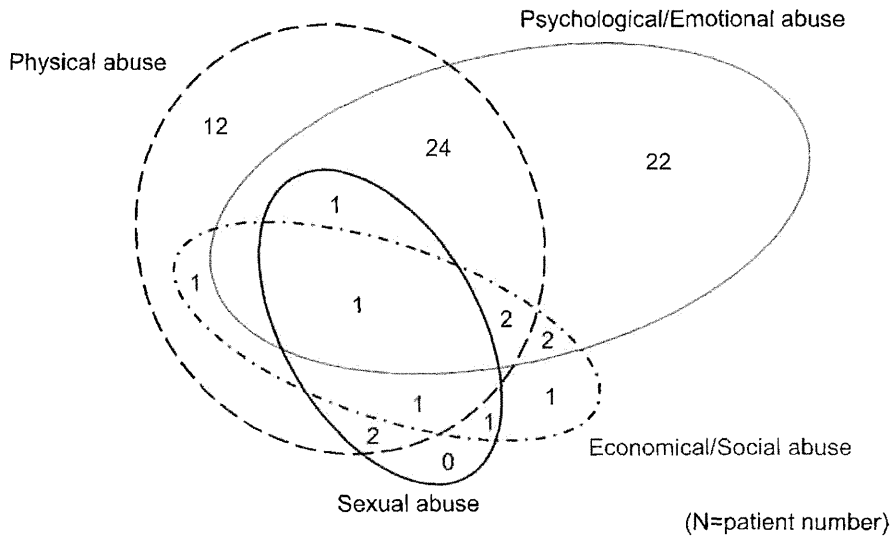

Figure 1 Combined IPV factors
The four factors (Physical, Emotional/Psychological, Sexual, Social/Economical abuse) of IPV are often combined.

fell into a depressive state. She felt a sense of powerlessness and vague anxiety, lost her appetite and complained of insomnia. In addition, she had nausea and epigastralgia due to mental stress when her husband talked to her or forced sexual intercourse.

She was admitted to our hospital and began to improve mentally and physically with psychological relaxation and a combination of antidepressants and anxiolytics. During her hospital stay, her husband expressed his determination to change and made promises to improve his behavior, although past promises had never been kept and she had been betrayed many times. We explained the pathology of IPV to our patient but she stated that she also had "bad points" and decided to return to her husband. She was also afraid that she couldn't ask for help from her mother or official welfare institutions again because they had expressed strong opposition to her decision to remarry the same man. This caused her to feel isolated.

Several months later, she came back to our department with bruises on her arm which her husband caused by kicking her. She stated that she had made up her mind to divorce him again and needed evidence of violence for the legal proceedings. We referred her to the department of orthopedics in order to obtain photos of her injury and the medical certificate. She didn't have enough income to support herself so we referred her to social support services.

Case No. 2 was a 39-year-old female that complained of bulimia, headache and hypertension. She was 163.5cm tall and weighed 93.9kg with a body mass index of 35.1.

She was raised by her parents and her father was violent towards her mother and their children. When her father hit or threatened her, her mother ignored the situation. After she grew up, she had a psychological conflict with her mother as well as her father, based on these violent childhood episodes.

After she married, her husband became violent. Her husband hit and kicked her, and threatened her verbally with financial blockage. In addi-

tion, he restricted her behavior and forbade her from seeing relatives and friends. To cope with her stress, she began to overeat and vomit, and gradually gained 20kg. She complained of chronic headaches and suffered from hypertension due to obesity. Moreover, she sometimes hit her son when she became irritated.

In Case No. 3, the victim was a 38-year-old man who was abused verbally and controlled by his wife. It is apparent that almost all of our abused patients are women and they are commonly abused by their husbands or boyfriends. However, this was an outstanding contrasting case.

The victim was involved in a traffic accident and confined to a wheelchair. Having lost both his job and sexual function in the accident, his wife began to work instead of him and developed a negative attitude towards him. She stated that he was "useless" and restricted him from going out of the house and controlled his behavior with threats. This case might indicate a key point, the power structure in the pathology of IPV.

Discussion

IPV had serious influences on both physical (psychosomatic) and mental health of the patients who consulted our department, as shown in Table 4. IPV should always be counted as a crucial factor in female patients' background in PSM.

Table 3 shows that battered patients complain of various types of physical and psychological symptoms. In case No. 1, the IPV victim showed vague and varied symptoms and her chief complaint changed as time passed. It is sometimes difficult to find signs that are directly related to IPV. If patients visit our department with some physical symptoms, we must always consider the possibility of an IPV background, particularly when we encounter unnatural symptoms or injuries, suspicious reasons for visiting medical services, or patients with a frightened demeanor. In addition, each IPV factor is mutually overlapped as shown in Figure 1 and this makes the symptoms more complicated. We should screen for violent experiences by asking direct questions[21] or by inquiring about related beliefs and behaviors[22]. IPV victim cases should be diagnosed based on physical and psychological factors and PSM doctors are well trained with such expertise. Victims of IPV may sometimes be unaware of the fact of IPV, particularly emotional/psychological and social/economical abuse. Both victims and batterers should be informed that this type of behavior is illegal and should be given information about treatment programs[20].

Since IPV survivors suffer various symptoms, they might consult not only a PSM doctor but also a dermatologist due to urticaria and burns, an orthopedician due to bone fractures, a urologist due to pollakisuria, a gynecologist due to dyspareunia or an otolaryngologist due to a rupture of the ear drum, dizziness and tinnitus. Therefore, all kinds of primary health care professionals have to pay attention to this problem[23]-[25]. PSM doctors should sometimes orchestrate a network of clinicians to deal with IPV victims' symptoms efficiently. However, Morier-Genoud C, et al[26] states that the detection rate of IPV by physicians is insufficient and this can be related to a lack of awareness. PSM doctors in Japan should educate general physicians about the influences of IPV from their experiences and evidence[23]-[25]. Another reason for a low detection rate of IPV could be the barriers to disclosure by the survivor's feelings of shame, loyalty to their partner or intimidation by the perpetrator and fear of not being believed[27]. Low self-esteem, powerlessness and lack of information about services are also factors that influence female disclosure of IPV[28].

Figure 2 illustrates the structure of IPV. IPV results from the stereotypical concept of gender roles. It is related to the power structure and the abuse of power or the domination and victimiza-

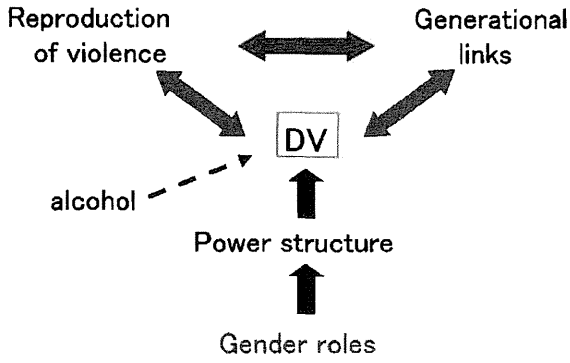

Figure 2 Structure of IPV
There is a cycle of violence. Sometimes the factor of alcohol consumption is added. There also exists a generational linkage: People who were subjected to physical and/or mental violence in their childhood might inflict violence upon their partner or children, because they do not know how to solve problems without violence. Conversely, it is well known that some victims of IPV tend to repeatedly choose partners who are violent. Thus, there is a reproduction of violence.

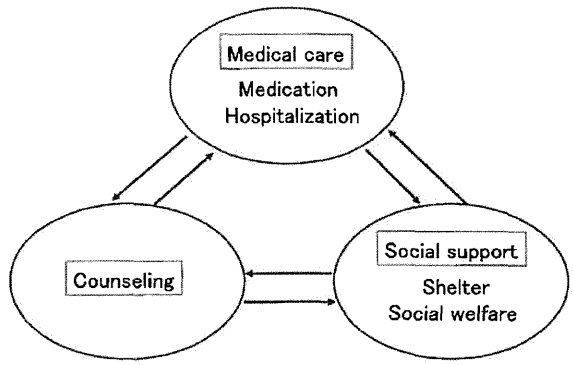

Figure 3 Coordination with facilities
Coordination with multiple facilities is important to support IPV victims.

tion of a physically or economically less powerful person by a more powerful person[20]. In general, the husband/boyfriend is the perpetrator and the wife/girlfriend is the victim, but it should be noted that partner abuse also occurs in homosexual relationships and in heterosexual relationships where men are the victims, as seen in case No. 3. In this case, the husband lost his job and sexual function and those unequal financial and health statuses created a situation in which the wife became the more powerful person, and exerted inappropriate control or intimidation over the husband.

Most researchers believe that abusive behavior is the result of multiple factors, including individual characteristics, a family history of violence, the culturally rooted belief that violence is an acceptable means of solving problems and that violence toward women is acceptable or tolerated[29]. Alcohol abuse is not causative but is often associated[30]. Previous studies showed that men who suffer from alcoholism combined with a major depressive disorder or antisocial personality disorder are more likely to commit IPV than men with either of these conditions alone[31,32].

Studies have not identified any consistent psychiatric diagnosis among batterers, but abusive men share some common characteristics such as rigid gender role stereotypes, low self-esteem, depression, a strong need for power and control, and violence in the family of origin, particularly witnessing parental violence[32]. In addition, some survivors of IPV are also survivors of an abusive childhood[33] and they have a tendency to choose consecutive abusive partners. For both batterers and survivors, patients who have a family history of violence may have low self-esteem and might believe that violence is the only way of resolving conflict. These are the generational links of violence and reproduction of violence. In case No. 2, the patient experienced abuse from her parents in her childhood. Her stress coping style was to over-eat and she had a tendency to violence towards her children. Her actions might come from her low self-esteem and a lack of confidence, experience and/or knowledge of problem solving methods other than violence. Therefore we should pay attention to not only evidence of ongoing and recent violence but also experiences of abuse in childhood[31].

PSM doctors can play a crucial role in a multidisciplinary team of doctors of several departments, nurses, pharmacists, dieticians and medical social workers in a hospital. Moreover, PSM doctors possess the means to refer victims to community resources such as shelters and legal aid[35)36)], and batterers to appropriate services for behavior modification interventions and treatment of comorbidities, such as depression and alcoholism[20)37)].

Figure 3 shows the importance of coordination with multiple facilities. When health care professionals cope with this problem, they can only prescribe their patients medication and/or hospitalization care. Although their patients' physical condition may improve, this is insufficient treatment overall. It is essential for IPV victims to be treated based on both physical and psychological aspects since they often need counseling for their psychological care and social support[38)]. For example, the patient in case No. 1 improved her physical condition with medication but needed social support for her economic state and long-term counseling to support her psychological recovery from trauma caused by IPV. Several previous studies showed those that reported emotional/psychological abuse only, and those that reported emotional abuse plus physical or sexual violence suggested the need for increased training of health care providers[39)40)]. Therefore the most important matter is to consider the multiple aspects of IPV and coordinate with appropriate facilities.

There are several methodological limitations of this study. First of all, the study was conducted with patients' comments. As several studies[27)28)] suggest, some IPV survivors and patients who have experiences of abuse in the present and/or in their childhood are not consciously or unconsciously aware of the severity and the meaning of their experience, and sometimes their memory and comments about the content of violence are psychologically biased. Some survivors may underestimate or deny their experience while others may exaggerate it. However, there is still some psychological meaning in their comments. What they have told us is what they believe to be true even if it were underestimated or exaggerated.

Second, as a narrative method was used in our study, some patients may have concealed their experiences in order to refuse participation in this study. We are restricted to checking the survivor's physical conditions at our hospital only and do not have the right to investigate whether patients are being truthful or not. Participants were limited to patients who were aware of their experiences of abuse and had the intention to talk about it. This possibility of bias cannot be completely ruled out and we consequently planned this study as a qualitative examination, not a quantitative one. Finally, an obvious limitation of the present study is its correlative investigation between abused experience and patients' symptoms, which allows no clear conclusion as to the causal directions of the relationship.

Although our study has several limitations, some highly suggestive results were seen as helpful information for clinical health providers and suggesting future studies. In order to help the survivors of IPV and promote women's health, further research addressing the present study's limitations is necessary.

In conclusion, this study focused on the health impact of IPV on patients who visited the department of PSM and provided preliminary findings of the characteristics of IPV in Japan. Survivors of IPV suffer various acute and chronic physical health problems and frequent mental distress such as depressive mood and anxiety. IPV survivors show vague and varied symptoms that sometimes seem incomprehensible and unrelated psychosomatic symptoms. It is sometimes diffi-

cult to find signs that are directly related to IPV since IPV factors are combined and symptoms are complicated. IPV victims need to be diagnosed and treated based not only on physical issues but also psychological issues. PSM doctors can assist IPV victims in this area and play an important role in organizing a multidisciplinary team to support patients and in preventing recurrent violence.

There is also the possibility of generational links and reproduction of violence as the pathology of IPV. Routinely questioning patients about ongoing and recent violent experiences as well as any childhood abusive experiences might be a means to helping these women and referring them to the appropriate legal and community services. Early intervention might be effective to reduce the risks of experiencing violence and efforts to increase societal awareness of the problem of IPV may eventually decrease the incidence of IPV and its medical complications.

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日本における成人女性に対する親密なパートナーからの暴力による健康被害と心療内科の果たす役割

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概要 目的：この研究の第一の目的は，親密なパートナーからの暴力（IPV）が成人患者の身体的，心理的状態に及ぼす健康被害を明らかにし，IPVの病理を明らかにすることである．また，第二の目的はIPV被害者の治療と臨床実践において，心療内科医の果たす役割を明確にすることである．

方法：2004年1月から2010年12月までに，当院心療内科を初診で受診した20歳以上のIPV被害者について研究を行った．すべての患者に対して，広範囲な健康に関しての質問をすると同時に，暴力を受けた経験について質問した．また，半構造化面接を行い，うつ状態自己評価尺度（SDS）と状態-特性不安検査（STAI）を施行した．

結果：IPV被害者は様々な急性および慢性の身体的健康問題と，しばしば抑うつ気分や不安などの精神的困難をかかえていた．患者は時にはあいまいな，あたかも直接の暴力事象とは無関係のように見受けられる症状を訴えることがあった．IPVの4つの因子（身体的，心理的，性的，経済的/社会的側面）はしばしば複合していた．

結論：IPVの病理は権力構造に基づいたもので，しばしば世代間連鎖と暴力の再生産をもたらしていた．IPVは急性，慢性にわたるさまざまな身体的・心理的健康被害をもたらすので，IPV被害者の診断，治療には心身両面からのアプローチが必要であり，心療内科医が果たす役割は非常に大きい．また，訴える症状があいまいであったり，複数の科に関連する場合も多いので，心療内科医が一般診療科の医師へのIPVに関する啓蒙とその診療のコーディネイトをはかり，院内においてはソーシャルワーカーなどを含む多職種のチーム医療の要となり，外部では複数の関係機関との連携を積極的に行う必要がある．このようにIPV被害者の診療には心療内科医が早期から関わることの重要性が示唆された．

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Severe Acute Interstitial Lung Disease After Crizotinib Therapy in a Patient With *EML4-ALK*–Positive Non–Small-Cell Lung Cancer

Introduction

The development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) such as erlotinib and gefitinib, and, more recently, that of the anaplastic lymphoma kinase (ALK) TKI crizotinib, has had a profound impact on the treatment of advanced non–small-cell lung cancer (NSCLC).[1-3] The occurrence of EGFR-TKI–associated interstitial lung disease (ILD) in patients with NSCLC has been found to be more frequent among Japanese patients than among white patients.[4,5]

Case Report

A 39-year-old male current-smoker (30 pack years) of Japanese descent was diagnosed with poorly differentiated stage IV lung adenocarcinoma (T4N3M1b) with multiple pleural dissemination as well as intra-abdominal lymph node and brain metastasis. Mutation analysis of biopsied tumor tissue showed that the tumor was wild type for the *EGFR* gene. Fluorescence in situ hybridization analysis with break-apart probes for the *ALK* gene revealed the presence of an *ALK* rearrangement, and subsequent reverse transcription and polymerase chain reaction analysis confirmed the presence of transcripts for variant 1 of the echinoderm microtubule-associated-like protein-4 gene (*EML4*) –*ALK* fusion gene. The patient received one cycle of chemotherapy with paclitaxel and carboplatin, but treatment was then withdrawn because of disease progression. As a second-line treatment,

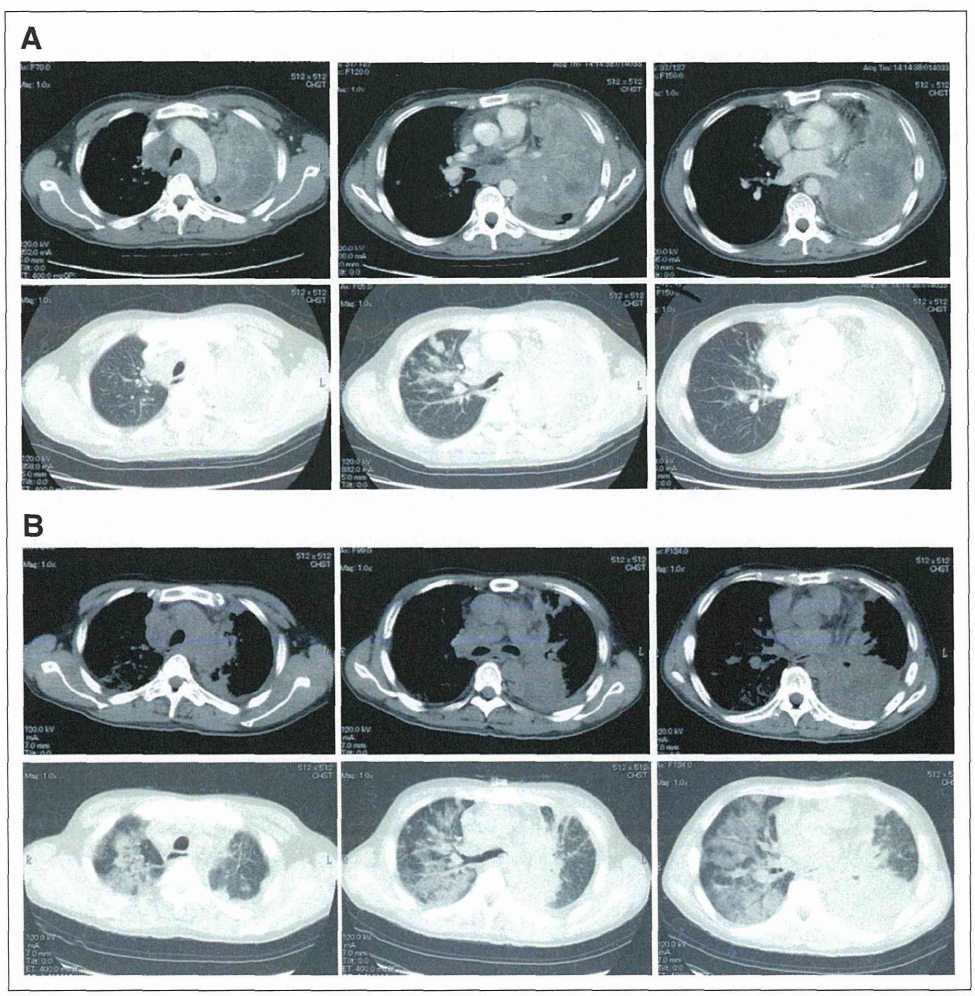

Fig 1.

crizotinib was administered orally at a dose of 250 mg twice daily. After 9 days of crizotinib, the patient developed acutely deteriorating dyspnea without demonstrable infection. With the patient breathing oxygen via a mask at a flow rate of 10 L/min, arterial blood gas determination revealed a P_aO_2 of 61.5 mmHg, a P_aCO_2 of 36.0 mmHg, and a pH of 7.46. A computed tomography scan of the chest showed extensive bilateral ground-glass opacities throughout both lungs, despite obvious shrinkage of the primary tumor lesions in his left lobes (Fig 1A, before crizotinib; Fig 1B, after crizotinib [day 9]). Crizotinib treatment was immediately discontinued, and methylprednisolone pulse therapy (1 g once per day for 3 days) was initiated. Empirical treatment with meropenem, ciprofloxacin hydrochloride, and trimethoprim-sulfamethoxazole was also administered. The patient nevertheless developed acute lung injury in accordance with the Lung Injury Score definitions,[6] and he died 21 days after his first administration of crizotinib. Postmortem analysis of a specimen of the right lung by hematoxylin-eosin (HE) staining revealed juvenile fibroblast hyperplasia (black arrow), nuclear swelling of aberrant alveolar cells (white arrow), and mild infiltration of inflammatory small round cells and neutrophils (Fig 2). The patient was thus diagnosed with diffuse alveolar damage, as previously described for individuals with severe EGFR-TKI–associated ILD.[7,8] No evidence of infection or of other specific etiologies was found. It can be difficult to make a diagnosis of pulmonary toxicity in lung cancer patients because of the high incidence of preexisting lung disease, respiratory tract infections, and progressive malignancy. Despite his smoking history, our patient did not have any preexisting pulmonary fibrosis or chronic obstructive lung disease. He developed rapidly progressive dyspnea with severe hypoxemia and diffuse interstitial infiltrates, which were detected radiographically 9 days after the onset of treatment with crizotinib. The histologic characteristics of his lung tissue were consistent with diffuse alveolar damage, thus opening up the possibility of various potential etiologies. An infectious etiology was ruled out by extensive microbiologic analysis of sputum and blood cultures and by the postmortem examination of the lungs. The pathologic analysis of lung tissue did not reveal any lymphangitic spread of the cancer. The patient's history and clinical examination did not provide any evidence of a toxic origin, prior radiotherapy, collagen vascular disorders, or other usual causes of adult respiratory distress syndrome. The exclusion of these other causes indicated that the severe ILD was most likely attributable to crizotinib treatment. Written informed consent was obtained from the patient's family for publication of this case report and accompanying images.

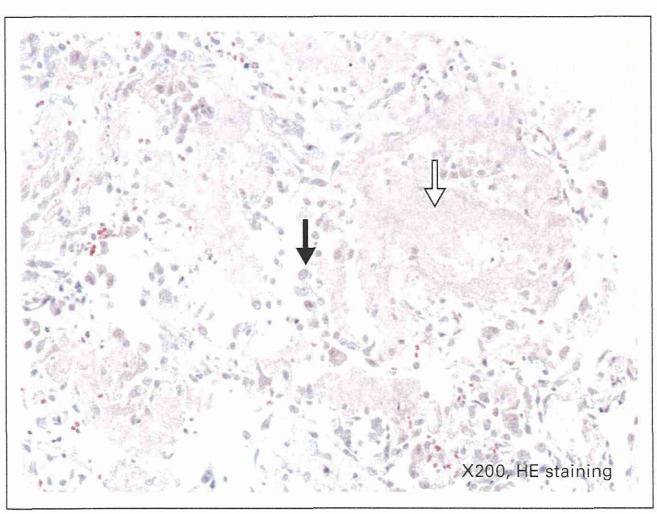

Fig 2.

Discussion

EML4-ALK was recently identified as a transforming fusion gene in NSCLC.[9,10] Preclinical and clinical studies have shown that cancer cells harboring *EML4-ALK* are highly sensitive to ALK inhibition.[3,11] Crizotinib is the first clinically available ALK-TKI and competes with ATP for binding to the tyrosine kinase pocket of the enzyme, inhibiting tyrosine phosphorylation of activated ALK at nanomolar concentrations. On the basis of its pronounced clinical activity and tolerability profile, crizotinib was approved by the US Food and Drug Administration to treat *ALK* rearrangement–positive NSCLC in August 2011. As far as we are aware, our patient is the first reported example of histologically documented crizotinib-associated ILD. Although crizotinib is generally well tolerated, physicians should thus be aware of the possibility of such a severe adverse reaction and full informed consent for treatment should be obtained. We have previously identified male sex, a history of smoking, and coincidence of interstitial pneumonia as independent risk factors for EGFR-TKI–associated ILD[12]; however, it remains unclear whether these risk factors also apply to crizotinib-associated ILD. Given that drug-induced ILD has a high associated mortality, a systematic survey allowing direct determination of the prevalence of and identification of risk factors for crizotinib-induced ILD is warranted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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