＜呼吸器内科＞

①薬剤リンパ球刺激試験が陽性となったミノサイクリンによる好酸球性肺炎の1例

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薬剤リンパ球刺激試験が陽性となったミノサイクリンによる好酸球性肺炎の1例

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Ⅰ．緒　　言

薬剤性肺障害はさまざまな薬剤で起こるとされ，その臨床病型，画像，病理所見は多様である。

原因として抗悪性腫瘍，リウマチ薬，抗菌薬，漢方など多くの報告があり，すべての薬剤に可能性があるとされる。

被疑薬の同定には同薬の再投与がもっとも有用とされるが，倫理的な問題もある。その一方で薬剤リンパ球刺激試験（DLST: drug lymphocyte stimulation test）は以前より本邦で行われており，中でもとくにミノサイクリン（MINO）によるものではDLSTは陰性になることが多いといわれている。

今回われわれはMINOのDLSTが陽性となった薬剤性肺障害を経験した。DLSTにはさまざまな問題点が指摘されている[1),2)]が，その意義を考える上で非常に示唆に富む症例と考え，文献的考察を踏まえここに報告する。

Ⅱ．症　　例

症　例：58歳，男性。

主　訴：呼吸困難。

既往歴：アレルギー性鼻炎，高血圧，脂質異常症，脳梗塞。

家族歴：特記事項なし。

アレルギー歴：特記事項なし。

喫煙歴：なし。

飲酒歴：機会飲酒。

現病歴：X年8月末より倦怠感，咳嗽が出現し，9月初旬より38℃台の発熱を伴いアジスロマイシン（AZM）を投与されたが，発熱が持続するため近医を受診した。気管支炎としてアンピシリン／スルバクタム（ABPC/SBT）の投与を開始されたが，解熱を認めず，メロペネム（MEPM）の点滴とMINOの内服へと変更された。その後，いったんは解熱していたが，X年10月に入ると40℃の発熱と労作時呼吸困難を認め，酸素投与も必要となってきたことから精査加療目的に10月7日当科に入院した。

入院時現症：身長169 cm，体重68.9 kg，意識清明，体温38.4℃，血圧107/71 mmHg，脈拍数102回／分整，呼吸数30回／分，SpO_2 93%（鼻カニュラ3 L/min）。胸部聴診上，肺野にcoarse crackles聴取。心音はⅠ音（→），Ⅱ音（→），Ⅲ（－），Ⅳ（－）。四肢には皮疹・関節痛・腫脹なく，ばち状指やチアノーゼも認めなかった。

血液検査・尿検査所見（表1）：好酸球の上昇を伴った白血球高値を認めるとともに，CRP，ASTとALT，IgEの上昇も認めた。KL-6は正常範囲内であった。

画像所見：胸部X線写真（図1A）では両側肺野にびまん性にすりガラス状陰影を認めた。

胸部単純CT（図1B）で両側肺野に広範なすりガラス状陰影，浸潤影の混在した像を認めた。

治療経過：X年10月7日に当科に入院し，気管支鏡検査を施行した。気管支肺胞洗浄液では生理食塩水90/150 mlの回収が得られ，細胞数が5.66×10^5/mlであり，マクロファージが43.7%，リンパ球が23.0%，好中球が1.8%，好酸球が32.5%であり，好酸球増多を認めた。細菌培養では有意な菌は認めず，抗酸菌塗抹やPCR検査はともに陰性であった。細胞診でも異型細胞など認めず，画像所見とあわせて急性好酸球性肺炎と診断した。経過とこれまでの症例報告から抗菌薬，その中でもMINOが第一の被疑薬と考えた。MINOやMEPMのDLSTを提出し

表1　血液検査・尿検査所見

WBC	10,400 /μl	T-Bil	0.61 mg/dl	IgM	64 mg/dl
Ne	71 %	AST	76 IU/L	IgE	575 IU/ml
Ly	9.5 %	ALT	124 IU/L	MPO-ANCA	(−)
Mo	4.5 %	LDH	259 IU/L	PR3-ANCA	(−)
Eo	15 %	TP	5.5 g/dl	KL-6	329 U/ml
Ba	0 %	ALB	2.1 g/dl	HbA1c	6.1 %
RBC	409×10⁴ /μl	BUN	13.2 mg/dl	DLST （ミノサイクリン）	
Hb	12.3 g/dl	Cr	0.67 mg/dl	Stimulation index （+） 250%	
Hct	36.8 %	Na	134 mEq/L		
MCV	90 fl	K	4.33 mEq/L	［尿検査］	
Plt	30.5×10⁴ /μl	Cl	98.9 mEq/L	混濁	(1+)
		PCT	0.23 ng/ml	比重	1.017
PT秒	14 秒	CRP	17.1 mg/dl	pH	6
PT%	61.1 %	T-spot	(−)	白血球	(−)
APTT	38.7 秒	抗核抗体	(−)	潜血	(1+)
D-dimer	2.32 μg/ml	RA	(−)	蛋白質	(−)
		IgG	1,130 mg/dl	ブドウ糖	(−)
		IgA	217 mg/dl	ケトン体	(−)

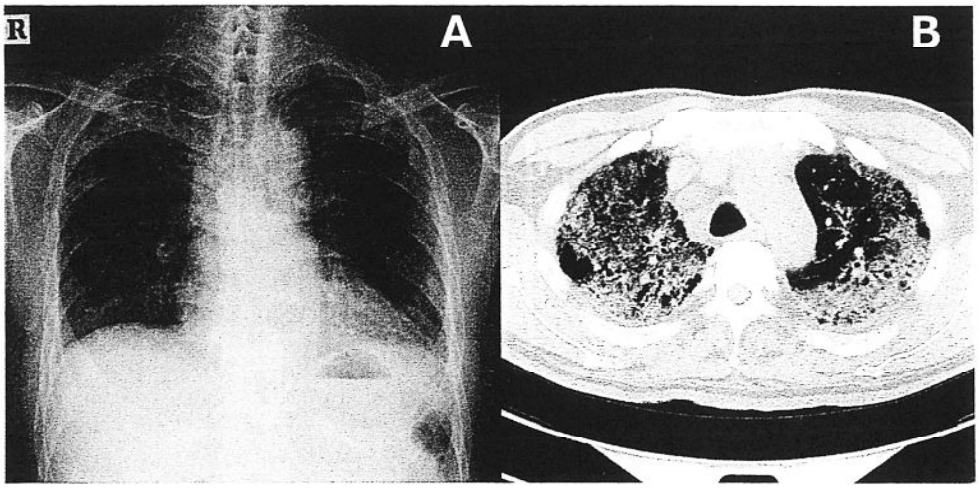

図1

A：両側肺野にびまん性すりガラス状陰影を認める。
B：両側に広範な浸潤影とすりガラス影の混在を認める。

た上で，被疑薬の中止とステロイドパルス療法を開始した（図2）。パルス終了後はプレドニン（PSL）30 mg/day の内服に切り替えた。治療開始とともに速やかに解熱は得られ，以後発熱もなく，酸素投与も終了できた。第14病日の胸部X線写真においても両側のびまん性のすりガラス状陰影は改善傾向であった。後日DLSTの結果（表1）が判明し，MINOのみ陽性であった。その後は漸減終了し，PSL終了時の胸部X線写真，CTでは陰影は消失していた（図3A，B）。以後は症状の再燃や胸部X線写真の増悪は来していない。

Ⅲ．考　　察

薬剤性肺障害は原因となる薬剤の投与歴があること，薬剤に起因する臨床病型の報告があること，ほかの原因疾患が否定されること，薬剤の中止による病態の改善があることで診断される。臨床的には咳嗽，息切れ，呼吸困難や皮疹の出現などが認められる。画像的にも胸部CTではびまん性肺障害，器質化肺炎，非特異性間質性肺炎，好酸球性肺炎，過敏性肺炎などあらゆるパターンをとるとされ，治療には被疑薬の中止が必須であり，ステロイド投与も行われている。

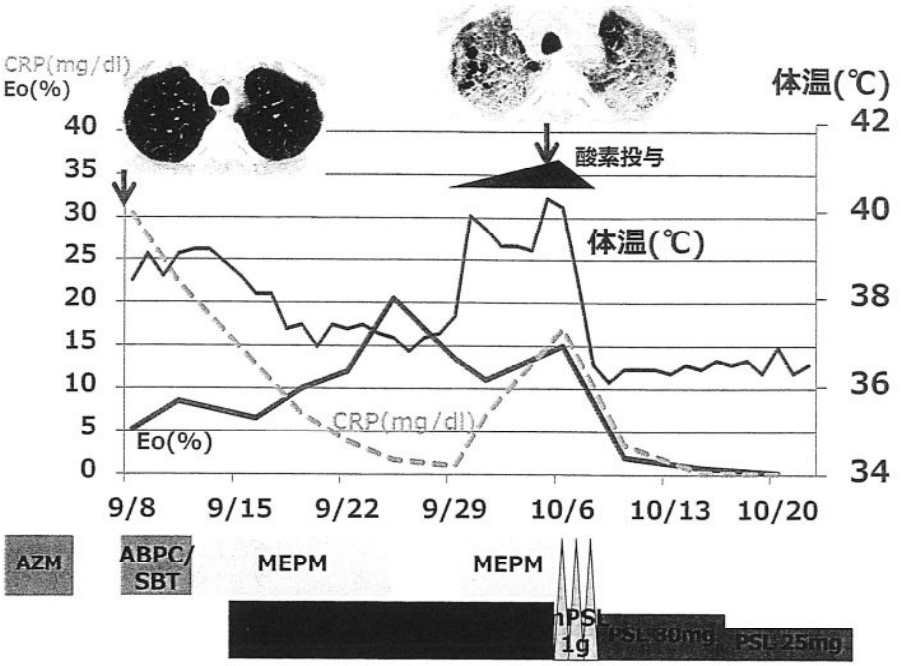

図2　臨床経過

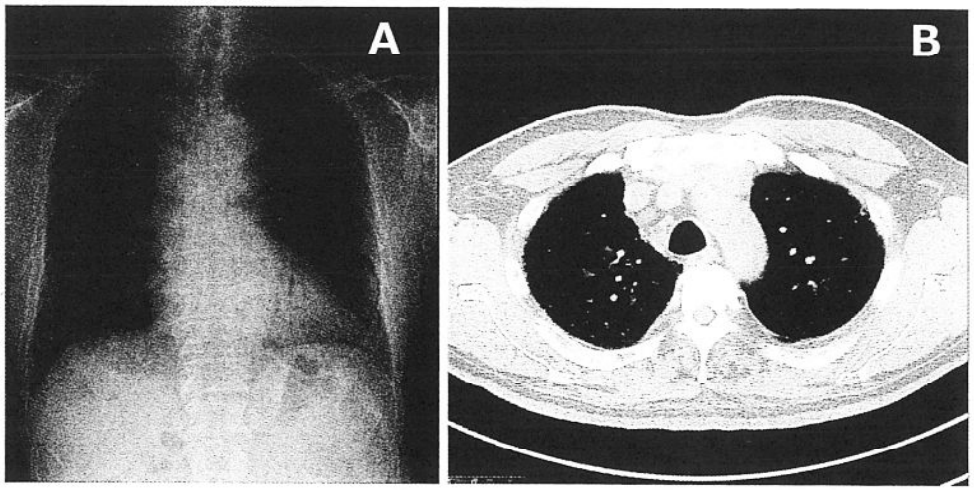

図3　ステロイド終了後の胸部X線写真（A），胸部単純CT（B）。ともに両側のすりガラス状陰影が消失している。

その中でもとくに薬剤性好酸球性肺炎はTh2細胞からのIL-5を代表とするサイトカインの産生が好酸球誘導に関与するといわれる[3),4)]が，詳細な機序は不明である。診断には，肺に異常を伴い末梢血中の好酸球の増加があること，肺組織への好酸球浸潤があること，気管支肺胞洗浄液中の好酸球増多があること，これら3点のうちいずれか1項目が認められることが必要である。本症例はこのうち2項目を満たしていることから診断した。原因薬剤としてアンカロン，ブレオマシイン，カプトプリル，金製剤などでの報告が多いが，すべての薬剤で起こる可能性がある。その臨床病型は急性の経過を示す急性好酸球性肺炎型と亜急性・慢性の経過を示す慢性好酸球性肺炎型に分けられる。いずれであっても可能な限り被疑薬を中止して病勢の推移を観察することが重要となる。

今回使用したMINOの経口薬は1971年に発売され，広域なスペクトラムを有し，広い年齢層で多くの感染症に使用されている抗菌薬である。抗菌薬による薬剤性肺炎ではマクロライド系[5)]やニューキノロン系[6)]での報告もあるが，MINO[7)]によるものが比較的多い。

これまで抗悪性腫瘍，リウマチ薬，抗菌薬，漢方など全175例の薬剤性肺障害に対して行われた検討ではDLSTの陽性率は66.9%[8]であった。そのうち，抗菌薬の陽性率は58.0%であった。その一方で，妹川ら[9]の報告ではMINOによる好酸球性肺炎でDLSTが陽性となったのは2例／12例（16.7%）と低率であった。これはMINO自体にリンパ球抑制作用があるためとされる。機序としてT細胞の活性に不可欠なCa^{2+}の流入を妨げることが関係していると考えられる[10]。実際にその抗炎症作用やコラゲナーゼ産生抑制作用に注目してMINOが関節リウマチの治療に有用[11]とする報告もある。

今回の症例のように複数の薬剤を投与中に増悪する肺炎に好酸球上昇を伴う例では積極的に薬剤性肺障害を疑い，原因薬剤の検索を進めながら速やかに気管支鏡検査を行うべきである。また，DLSTについては意義が乏しいとする意見もある一方で，国内では広く普及している。本症例ではリンパ球抑制作用があるとされるMINOでDLSTが陽性を示したことから，確定診断の根拠とした。薬剤再投与は倫理的な問題も含み困難であるからこそ，DLSTの解釈と限界を含め十分な検討を行っていくことが重要である。

Ⅳ．結　　語

今回われわれはリンパ球機能抑制作用をもつとされるMINOでDLSTが陽性であり，より強くその関与を疑った好酸球性肺炎の1例を経験したのでここに報告する。

なお本症例は2015年（平成27年）7月4日開催の第53回日本呼吸器学会　中国・四国地方会（松山市）で発表した。

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（受付　2015－8－11）

＜呼吸器内科＞

①Mustard gas exposure and mortality among retired workers at a poisonous gas factory in Japan: a 57-year follow-up cohort study

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ORIGINAL ARTICLE

Mustard gas exposure and mortality among retired workers at a poisonous gas factory in Japan: a 57-year follow-up cohort study

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ABSTRACT

Objectives Mustard gas (MG) has been the most widely used chemical warfare agent in the past century. However, few but conflicting data exist on the effects of MG exposure on long-term mortality. We investigated MG-related mortality in retired workers at a poisonous gas factory.

Methods We assessed mortality rates among 2392 male and 1226 female workers, whose vital status could be determined through 31 December 2009, at a poisonous gas factory operating from 1929 to 1945 in Okuno-jima, Japan. The analysis employed standardised mortality ratios (SMRs) calculated using national and prefectural references and a Cox proportional hazard regression model. Applying the Kaplan-Meier method, we compared cumulative death rates in the study cohort stratified by an 'Okuno-jima MG Index' which represented the product of HRs derived for job category and length of service.

Results Among male workers, we found significant excesses in mortality from upper respiratory tract cancer (SMR 3.06), liver cancer (1.67), lung cancer (2.01) and chronic bronchitis/emphysema (4.84) compared with the national population, as well as stomach cancer (1.20) versus the Hiroshima Prefecture population. When stratified into 3 subgroups by the Okuno-jima MG Index, those with a higher Okuno-jima MG Index had significantly higher cumulative rates of death from respiratory cancer and chronic bronchitis/emphysema.

Conclusions MG exposure significantly increases the long-term risk of death from respiratory cancer and chronic bronchitis/emphysema. The Okuno-jima MG Index may be a useful indicator for estimating cumulative MG exposure.

What this paper adds

- There have been few but conflicting data available on the effects of mustard gas exposure on long-term mortality.
- We assessed the mortality of 2392 male workers at a poisonous gas factory in Japan over a 57-year period, and found a statistically significant causal relationship between mustard gas exposure and death from chronic bronchitis/emphysema and respiratory cancer.
- The significance of a new index to estimate individual cumulative mustard gas exposure at this factory was determined.

INTRODUCTION

Although the usage of chemical weapons dates back to the eras of ancient China and Greece, their usage as weapons of mass destruction began during the World War I. Since the initial use of chlorine by German Forces in 1915, ~40 types of chemical warfare agents, such as phosgene, hydrogen cyanide and diphenylcyanoarsine, have been employed in combat.[1] Mustard gas (MG) was the most extensively used chemical agent during the World War I and inflicted injury on ~400 000 individuals, a number equivalent to almost 77% of all victims of chemical agents.[2] Despite the ban on chemical warfare agents mandated by the Geneva Protocol in 1925, MG was used subsequently on several occasions. Most recently, the Iraqi Army employed MG against Iranian soldiers and civilians during the Iran–Iraq war of the 1980s, resulting in injuries to over 100 000 victims.[3]

MG or sulfur mustard (bis (2-chloroethyl) sulfide) is mainly absorbed by inhalation and through the skin or the anterior surface of the eyes, including the cornea and the conjunctiva. On contact, MG exerts its toxicity through an irreversible alkylation of cellular proteins and nucleic acids.[4 5] Classified as a blistering agent, MG is recognised as having potent mutagenic, carcinogenic and radiomimetic properties.[6] MG might have subsequent systemic action on the nervous, cardiac and digestive systems following absorption.[7]

From 1929 to 1945, the Japanese Army operated a poisonous gas factory in Okuno-jima, a small island located in the Inland Sea of Japan in the city of Takehara in Hiroshima Prefecture.[8–10] In this factory, several types of poisonous gas, such as MG, lewisite, diphenylcyanoarsine, hydrocyanic acid, phosgene and chloroacetophenone, were produced. Of the gases, MG was the most poisonous and was produced in the largest quantities, reaching about 450 tons at peak production.[9] Despite wearing protective masks and clothing, the factory workers were chronically exposed to MG due to poor industrial hygiene practices that were prevalent in wartime Japan.

The two basic types of MG exposure include: (1) single high-dose exposure on the battlefield, and (2) long-term repeated exposure in MG factories. In epidemiological studies of soldiers exposed to MG during the World War I, a single exposure to MG appeared to increase mortality from lung cancer and respiratory disease somewhat, but the incremental risk was not large and the causal association with MG exposure was unclear.[11–13] In contrast, epidemiological studies of workers in MG factories have suggested a significant increase in mortality due to cancers of the upper respiratory tract, lung, oesophagus, stomach and bladder, and leukaemia, as well as non-malignant respiratory disease.[8 14–17] However, among the malignancies, only cancers of the upper respiratory tract and lung were proven to be associated with MG exposure. While the poisonous gas factory workers in Okuno-jima represent one of the few cohorts globally who can provide valuable information, only mortality due to respiratory cancer has been studied in this population.[8 16] Accordingly, the present study analysed and characterised mortality in the Okuno-jima cohort over a 57-year period with the aim of clarifying the association between MG exposure and mortality.

METHODS

Study population

Former workers at the poisonous gas factory in Okuno-jima comprise two major groups: (1) individuals who had worked at the factory between 1929 and 1945, and (2) those who had engaged in the disposal of poisonous gas stockpiled after the World War II between 1945 and 1948.[9] As of 31 December 2009, 6876 participants (3865 males and 3011 females) were registered as former workers at the poisonous gas factory in Okuno-jima. We restricted the study cohort to the 2392 male and 1226 female workers who had visited the Tadanoumi Branch of the Kure Kyosai Hospital (Tadanoumi Hospital) since 1952 and whose vital status as of the end of 2009 could be determined (see online supplementary figure S1). Tadanoumi Hospital is located in Takehara City on Honshu, a short distance across the Inland Sea from Okuno-jima, and was established in 1942 for the purposes of providing medical care to the poisonous gas factory workers. We have evaluated the factory workers for adverse health effects at this hospital since 1952. This study cohort constitutes about 62% (2392/3865) of the male and 41% (1226/3011) of the female factory workers.

This study was approved by the Ethics Committee of the Hiroshima University.

Data collection

Reviewing the medical records and death certificates stored at the Tadanoumi Hospital, we obtained information on the vital status, sex, dates of birth and death, job category at the factory, dates of employment, length of service, smoking status and cause of death for each worker. Personal data were managed carefully to protect anonymity. Causes of death were abstracted from the death certificates and assigned according to the International Classification of Diseases, 10th Revision (ICD-10). The 20 causes of death listed in table 1 were chosen from the preliminary analysis. On the basis of their specific jobs, the workers were categorised into one of three groups.[8] Group A consisted of workers who had engaged directly in the production or disposal of MG, whereas group B comprised those who had been exposed to MG in laboratories or during repairs or inspections of the factory. Group C consisted of workers who had participated in either the production or disposal of other gases or medical or administrative work. This last group also included students who had been recruited for service in Okuno-jima. Based on the nature of the work involved, the risk of MG exposure was considered to increase across the job categories in the following order: group A>group B>group C.

Table 1 SMRs for major causes of death in the study cohort of 2392 male workers based on the Japanese and Hiroshima male population standards, 1952–2009

Cause of death (ICD-10 codes)	O	E	SMR (95% CI) based on: National rates	Hiroshima rates
All causes (A00-U89)	1959	2214.7	0.88 (0.85 to 0.92)	0.92 (0.88 to 0.96)
Malignant neoplasms (C00-C97)	772	582.2	1.33 (1.23 to 1.42)	1.36 (1.26 to 1.46)
Upper respiratory tract (C00-C14, C30-C32)	45	14.7	3.06 (2.23 to 4.09)	–
Oesophagus (C15)	20	26.2	0.76 (0.47 to 1.18)	1.08 (0.65 to 1.69)
Stomach (C16)	183	169.3	1.08 (0.93 to 1.25)	1.20 (1.03 to 1.39)
Colon and rectum (C18-C21)	50	51.9	0.96 (0.72 to 1.27)	–
Liver (C22)	101	60.4	1.67 (1.36 to 2.03)	1.31 (1.06 to 1.60)
Pancreas (C25)	31	29.0	1.07 (0.73 to 1.52)	1.20 (0.82 to 1.71)
Lung (C33, C34)	230	114.2	2.01 (1.76 to 2.29)	2.04 (1.79 to 2.32)
Skin (C43, C44)	2	2.0	0.99 (0.12 to 3.56)	–
Urinary organs (C64-C68)	19	19.5	0.98 (0.59 to 1.53)	–
Lymphopoietic (C81-C96)	30	27.1	1.11 (0.75 to 1.58)	1.18 (0.70 to 1.86)
Circulatory diseases (I00-I99)	480	811.2	0.59 (0.54 to 0.65)	–
Ischaemic heart diseases (I20-I25)	69	147.4	0.47 (0.36 to 0.59)	0.54 (0.42 to 0.69)
Cerebrovascular diseases (I60-I69)	202	422.6	0.48 (0.41 to 0.55)	0.57 (0.49 to 0.65)
Respiratory diseases (J00-J99)	407	288.7	1.41 (1.28 to 1.55)	–
Pneumonia (J12-J18)	158	173.4	0.91 (0.77 to 1.06)	0.92 (0.78 to 1.08)
Chronic bronchitis and emphysema (J40-J43)	159	32.8	4.84 (4.12 to 5.66)	4.16 (3.54 to 4.86)
Interstitial pulmonary diseases (J84)	18	12.8	1.41 (0.84 to 2.23)	–
Digestive diseases (K00-K93)	65	117.5	0.55 (0.43 to 0.71)	–

E, expected number of deaths; ICD-10, International Classification of Diseases, 10th Revision; O, observed number of deaths; SMR, standardised mortality ratio.

Calculation of SMR

Standardised mortality ratios (SMRs) were computed for each major cause of death by dividing the observed number of deaths by the expected number of deaths. For each cause, the expected number of deaths was calculated as the sum of the products of the sex-specific, age-specific and period-specific number of person-years and the corresponding rates reported for the general Japanese population. For each SMR, a 95% CI was calculated based on the assumption that the observed number of deaths followed a Poisson distribution.[18]

We also calculated SMRs based on the general population of Hiroshima Prefecture, the primary location of residence for the majority of poisonous gas factory workers. SMR analyses were limited to the period 1952–2009 because there were no medical records for workers who had died before 1952 at the initiation of our investigation. For the causes of death with SMRs significantly exceeding the national or Hiroshima Prefecture population rates, SMR analyses were performed with stratification of the study cohort by job group, length of service and calendar period.

Statistical analysis

Using a Cox proportional hazard regression model, univariate and multivariate analyses were performed to examine the relationships between the risk of cause-specific death and job group and length of service. Both factors were considered to be related to the intensity and duration of MG exposure. The duration of follow-up was calculated from the date of employment at the factory until death or the end of the study on 31 December 2009, whichever came first. The duration of time between employment at the factory and death from the selected cause was regarded as the dependent variable, whereas job group, length of service, age at the time of employment and smoking status were designated as independent variables.

The attributable risk per cent was calculated as the difference in incidence between the specific group and the reference group divided by the incidence in the specific group, multiplied by 100.

The product of the adjusted HRs derived for the job groups in the Cox proportional hazard analyses and the length of service (the Okuno-jima MG Index) is considered to be a useful indicator for estimating the individual cumulative extent of exposure to MG. Accordingly, we then stratified the cohort on the basis of the Okuno-jima MG Index into three equal groups for which the cumulative mortality from the selected causes was estimated using Kaplan-Meier curves. Statistical analyses were performed using JMP V.9.0.2 software (SAS Institute, Tokyo, Japan). A p value <0.05 was statistically significant.

RESULTS

As of 31 December 2009, 433 male and 744 female workers were alive; 1959 male and 482 female workers had died (see online supplementary figure S1). Causes were known for 99.9% (2440/2441) of the deaths. During the period from 1952 to 2009, the cohort contributed a cumulative total of 157561.5 person-years (95067.5 person-years for males and 62 494 person-years for females) of follow-up. Among the participants, 694 males and 23 females belonged to group A, 793 males and 85 females to group B, and 903 males and 1117 females to group C. The job categories for three participants (two males and one female) were unknown. Characteristics of the male and female workers included in the study cohort are shown in online supplementary table S1.

Table 1 and online supplementary table S2 present the results of the SMR analyses for each major cause of death in the study cohort of 2392 male and 1226 female workers, respectively. Since mortality rates were not fully available, SMRs for the Hiroshima Prefecture could not be calculated for some causes of death. Compared with the national and Hiroshima Prefecture population reference rates, overall mortality in the male and female study cohorts was significantly lower than expected (SMR 0.88 and 0.92 for males, 0.69 and 0.72 for females, respectively).

The SMRs in male workers based on the national and Hiroshima Prefecture mortality rates revealed statistically significant excesses in cause-specific mortality for certain conditions, including upper respiratory tract cancers (SMR 3.06 vs the national rate; data not available for Hiroshima Prefecture), stomach cancer (1.08 and 1.20), liver cancer (1.67 and 1.31), lung cancer (2.01 and 2.04) and chronic bronchitis/emphysema (4.84 and 4.16). On the other hand, significant deficits were noted for ischaemic heart diseases (SMR 0.47 and 0.54), cerebrovascular diseases (0.48 and 0.57) and digestive diseases (0.55 vs the national rate; data not available for Hiroshima Prefecture). Tables 2 and 3 and online supplementary table S3 show the SMRs for the selected causes of death for the study cohort stratified by job groups and length of service (≤1; >1; ≤3; >3 years). The analyses of male workers revealed several trends. First, job categories conferring a greater risk for MG exposure were associated with higher SMRs for upper respiratory tract cancer, liver cancer, lung cancer and chronic bronchitis/emphysema, but not for stomach cancer. Second, there was a trend for longer length of service with higher SMRs for upper respiratory tract cancer, lung cancer and chronic bronchitis/emphysema. An exception to this trend was stomach and liver cancer.

Table 4 and online supplementary table S4 present the SMRs for the selected causes of death by calendar periods. Among male workers, the SMRs for upper respiratory tract cancer, lung cancer and chronic bronchitis/emphysema were highest for the

Table 2 SMRs for selected causes of death in the male study cohort by job category based on the Japanese male population standard, 1952–2009

Cause of death (ICD-10 codes)	Group A			Group B			Group C		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Upper respiratory tract cancer (C00-C14, C30-C32)	22	4.1	5.38 (3.37 to 8.15)	19	4.9	3.91 (2.35 to 6.10)	4	5.8	0.69 (0.19 to 1.78)
Stomach cancer (C16)	58	50.0	1.16 (0.88 to 1.50)	59	57.8	1.02 (0.78 to 1.32)	66	61.4	1.08 (0.83 to 1.37)
Liver cancer (C22)	30	16.0	1.88 (1.27 to 2.68)	34	19.7	1.73 (1.20 to 2.41)	37	26.2	1.41 (0.99 to 1.94)
Lung cancer (C33, C34)	93	30.9	3.01 (2.43 to 3.69)	77	37.2	2.07 (1.63 to 2.59)	59	46.1	1.28 (0.98 to 1.65)
Chronic bronchitis and emphysema (J40-J43)	63	9.6	6.59 (5.06 to 8.43)	63	11.3	5.58 (4.29 to 7.14)	32	11.9	2.68 (1.83 to 3.78)

E, expected number of deaths; ICD-10, International Classification of Diseases, 10th Revision; O, observed number of deaths; SMR, standardised mortality ratio.

Table 3 SMRs for selected causes of death in the male study cohort by length of service based on the Japanese male population standard, 1952–2009

Cause of death (ICD-10 codes)	≤1 year			>1 to 3 years			>3 years		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Upper respiratory tract cancer (C00-C14, C30-C32)	4	4.6	0.88 (0.24 to 2.25)	13	4.9	2.68 (1.43 to 4.58)	28	5.3	5.29 (3.51 to 7.64)
Stomach cancer (C16)	42	46.5	0.90 (0.65 to 1.22)	67	55.2	1.21 (0.94 to 1.54)	74	67.3	1.10 (0.86 to 1.38)
Liver cancer (C22)	26	21.7	1.20 (0.78 to 1.75)	41	20.2	2.03 (1.46 to 2.75)	33	19.9	1.66 (1.14 to 2.32)
Lung cancer (C33, C34)	54	36.6	1.48 (1.11 to 1.93)	78	39.2	1.99 (1.57 to 2.49)	97	38.3	2.53 (2.05 to 3.09)
Chronic bronchitis and emphysema (J40-J43)	22	8.8	2.50 (1.56 to 3.78)	51	11.1	4.60 (3.43 to 6.05)	85	12.9	6.59 (5.26 to 8.15)

E, expected number of deaths; ICD-10, International Classification of Diseases, 10th Revision; O, observed number of deaths; SMR, standardised mortality ratio.

Table 4 SMRs for selected causes of death in the male study cohort by calendar periods based on the Japanese male population standard

Cause of death (ICD-10 codes)	1952–1959			1960–1969			1970–1979		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Upper respiratory tract cancer (C00-C14, C30-C32)	5	0.8	6.52 (2.12 to 15.21)	9	1.8	4.90 (2.24 to 9.31)	8	2.9	2.77 (1.19 to 5.45)
Stomach cancer (C16)	6	13.0	0.46 (0.17 to 1.00)	23	29.6	0.78 (0.49 to 1.17)	49	38.0	1.29 (0.96 to 1.71)
Liver cancer (C22)	2	2.7	0.75 (0.09 to 2.69)	4	5.6	0.72 (0.19 to 1.83)	20	8.8	2.26 (1.38 to 3.50)
Lung cancer (C33, C34)	9	1.1	7.93 (3.63 to 15.05)	26	5.5	4.71 (3.07 to 6.90)	38	13.8	2.76 (1.95 to 3.78)
Chronic bronchitis and emphysema (J40-J43)	9	0.7	13.62 (6.23 to 25.86)	20	1.4	14.58 (8.91 to 22.52)	22	4.3	5.12 (3.21 to 7.75)
Cause of death (ICD-10 codes)	**1980–1989**			**1990–1999**			**2000–2009**		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Upper respiratory tract cancer (C00-C14, C30-C32)	11	3.2	3.49 (1.74 to 6.24)	6	3.4	1.78 (0.65 to 3.88)	6	2.7	2.22 (0.81 to 4.83)
Stomach cancer (C16)	50	36.4	1.37 (1.02 to 1.81)	34	31.2	1.09 (0.76 to 1.52)	21	21.1	1.00 (0.62 to 1.52)
Liver cancer (C22)	33	14.8	2.22 (1.53 to 3.12)	26	16.9	1.54 (1.00 to 2.25)	16	11.6	1.38 (0.79 to 2.25)
Lung cancer (C33, C34)	47	26.7	1.76 (1.29 to 2.34)	66	35.9	1.84 (1.42 to 2.34)	44	31.1	1.41 (1.03 to 1.90)
Chronic bronchitis and emphysema (J40-J43)	32	6.7	4.78 (3.27 to 6.74)	40	10.5	3.82 (2.73 to 5.20)	36	9.3	3.87 (2.71 to 5.35)

E, expected number of deaths; ICD-10, International Classification of Diseases, 10th Revision; O, observed number of deaths; SMR, standardised mortality ratio.

periods 1952–1959 and 1960–1969, but showed a trend for decreasing SMRs over the subsequent decades. The SMRs for stomach and liver cancer were significantly increased during the periods of 1980–1989 and 1970–1999, respectively.

Tables 5 and 6 and online supplementary table S5 show the results of the univariate and multivariate Cox proportional hazard analyses. Since the observed number of deaths due to upper respiratory tract cancer was relatively small, the mortality data for upper respiratory cancer and lung cancer were combined. In the Cox proportional hazard analyses of male workers, job group, length of service, age at employment and smoking status were all significantly related to the risk of death from respiratory cancer, while job group, length of service and age at employment were also significantly related to the risk of death from chronic bronchitis/emphysema. On the other hand, only the age at employment was significantly related to the risk of stomach and liver cancer mortality (see online supplementary table S6).

Regarding respiratory cancer death among male workers, the attributable risk per cent for groups A and B compared with that for group C was 74.6% and 63.6%, respectively, and the attributable risk per cent for smoking was 85.5%. Regarding chronic bronchitis/emphysema death among male workers, the attributable risk per cent for groups A and B compared with that for group C was 76.9% and 72.2%, respectively, and the attributable risk per cent for smoking was 76.9%.

Participants without data on smoking status (n=429), dates of employment (n=64), length of service (n=4) and job type (n=2) were excluded from the respective analyses.

We defined an indicator, the 'Okuno-jima MG Index', as the product of the HRs for the respective job group and length of service. (eg, In the case of a male worker in group A whose length of service was 12 months, the Okuno-jima MG Index for respiratory cancer death is the product of 1.86 and 12, or 22.32.) Among male workers, the median (IQR) of the distribution of the Okuno-jima MG Index was 2.95 (1.00–6.51) for respiratory cancer and 3.33 (1.00–7.90) for chronic bronchitis/emphysema.

The cumulative death rates for respiratory cancer and chronic bronchitis/emphysema were analysed by the Kaplan-Meier method using the Okuno-jima MG Index to divide the study cohort into three (high, middle, low) groups. For the male workers, within each disease category, the cumulative death rates differed significantly among the three groups (figure 1). Similarly, for female workers, the cumulative death rates for respiratory cancer showed marginally significant differences, and those for chronic bronchitis/emphysema differed significantly (see online supplementary figure S2).

DISCUSSION

Compared with the national and Hiroshima Prefecture populations, all-cause mortality rates were lower in the study cohort of 2392 male and 1226 female workers at the poisonous gas factory in Okuno-jima. In contrast, the analysis of male workers found significant excess mortality from cancers of the upper respiratory tract, stomach, liver and lung, as well as chronic bronchitis/emphysema. When the workers were categorised by

Table 5 Cox proportional hazards regression: factors associated with respiratory cancer death in the male study cohort

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Job group				
Group A	2.97 (2.18 to 4.06)	<0.0001	1.86 (1.29 to 2.69)	0.0008
Group B	2.08 (1.51 to 2.88)	<0.0001	1.47 (1.02 to 2.14)	0.0397
Group C	1.0		1.0	
Length of service	1.11 (1.08 to 1.14)	<0.0001	1.05 (1.01 to 1.09)	0.0145
Age at employment	1.07 (1.06 to 1.09)	<0.0001	1.07 (1.05 to 1.09)	<0.0001
Smoking status				
Smoker	2.06 (1.15 to 4.15)	0.0130	2.51 (1.40 to 5.10)	0.0012
Non-smoker	1.0		1.0	

Table 6 Cox proportional hazards regression: factors associated with chronic bronchitis/emphysema death in the male study cohort

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p Value	HR (95% CI)	p Value
Job group				
Group A	3.41 (2.24 to 5.29)	<0.0001	2.22 (1.44 to 3.49)	0.0003
Group B	2.85 (1.88 to 4.41)	<0.0001	1.82 (1.18 to 2.86)	0.0063
Group C	1.0		1.0	
Length of service	1.14 (1.10 to 1.18)	<0.0001	1.05 (1.01 to 1.09)	0.0184
Age at employment	1.15 (1.13 to 1.18)	<0.0001	1.15 (1.13 to 1.17)	<0.0001
Smoking status				
Smoker	1.10 (0.63 to 2.10)	0.7562		
Non-smoker	1.0			

job group (group A, B or C) in the order of increasing risk of MG exposure, the HRs for mortality from respiratory cancer or chronic bronchitis/emphysema in groups A and B were higher compared with that of group C. Furthermore, in the Kaplan-Meier analyses, the group with a higher Okuno-jima MG Index showed a significantly higher cumulative death rate for respiratory cancer and chronic bronchitis/emphysema. On the other hand, MG exposure was not significantly associated with mortality from stomach and liver cancer.

A key finding of this study is that chronic MG exposure significantly increases the risk of mortality from chronic bronchitis/emphysema as well as respiratory cancer. A mortality study in workers at an MG factory in the UK revealed significant excess mortality from respiratory cancer, oesophageal cancer and stomach cancer, as well as non-malignant respiratory disease; however, only respiratory cancer was proven to be associated with MG exposure.[14] Previous studies have established that the prevalence of chronic bronchitis/emphysema is higher among workers in the poisonous gas factory in Okuno-jima.[19 20] Similarly, the present analysis demonstrated that mortality from chronic bronchitis/emphysema was also significantly higher, indicating that chronic MG exposure significantly increases the risk of mortality from chronic bronchitis/emphysema as well as respiratory cancer. We believe that these diseases are caused by the exposure of the respiratory tract and lung parenchyma to MG through direct inhalation. Interestingly, mortality from chronic bronchitis/emphysema was still relatively high in the 2000s despite decreasing over the decades. This is most likely due to a cessation effect. This means that chronic bronchitis/emphysema caused by MG exposure is refractory and persistent and produces very prolonged health damage, suggesting the necessity of continuous medical intervention for this condition. More notably, the cumulative death rates for respiratory cancer and chronic bronchitis/emphysema increased significantly commensurate to increases in the Okuno-jima MG Index, an indicator which integrated job group and length of service into the risk for mortality. In previous studies of workers in MG factories, job category and length of service have been used as indicators to estimate the extent of MG exposure.[8 14 21 22] In this study, the SMRs for respiratory cancer and chronic bronchitis/emphysema tended to increase with the increasing risk of MG exposure as defined by job category as well as by length of service, suggesting that these two factors may reflect the extent of MG exposure. Applying the Okuno-jima MG Index as a grouping indicator, we found a statistically significant difference in the cumulative death rates for respiratory cancer and chronic bronchitis/emphysema. This strongly suggests that the Okuno-jima MG Index may more precisely reflect the extent of MG exposure.

Excess mortality from stomach cancer was observed in this study as well as in the study in the UK,[14] suggesting that MG exposure plays a potential role in the development of stomach cancer. Although swallowing saliva contaminated with MG may promote stomach cancer, the association between MG exposure and mortality from stomach cancer is left to be consisted. The retired workers of the poisonous gas factory in Okuno-jima have received regular, thorough medical examinations which include an upper gastrointestinal series. This most likely contributes to early detection and radical surgery among many workers, thereby reducing mortality from stomach cancer. Taking this situation into consideration, we speculate that the incidence of gastric cancer may be even higher than the

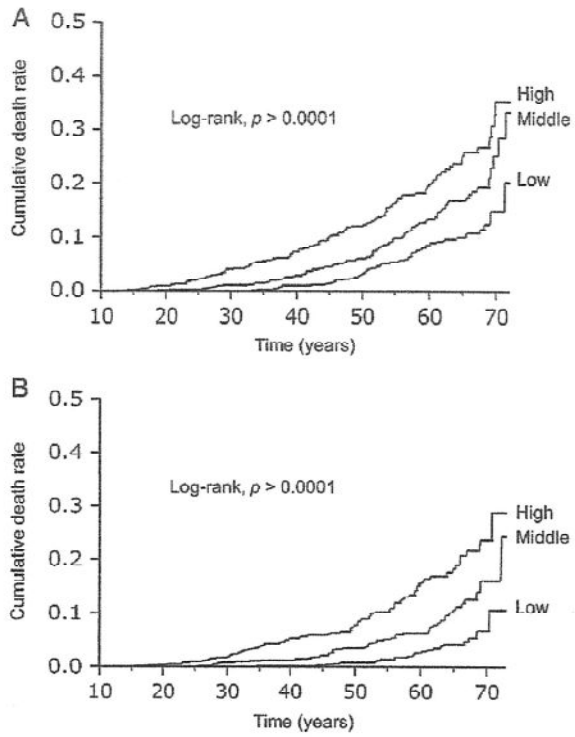

Figure 1 Cumulative death rates due to respiratory cancer (A) and chronic bronchitis/emphysema (B) in the male study cohort stratified by the Okuno-jima MG Index. Cumulative death rates differed significantly ($p<0.0001$, log-rank test) among the high, middle and low groups within both disease categories. MG, mustard gas.

associated mortality observed in this cohort. Regarding the excess SMR for liver cancer, it is impossible to provide a reasonable explanation, because information on other major aetiological factors, such as exposure to hepatitis viruses and alcohol, could not be obtained in this study. A previous epidemiological study in Hiroshima Prefecture demonstrated that the prevalence of hepatitis B and/or C virus infection was very high in the area where the Tadanoumi Hospital is located,[23] and thus we speculate that this might affect the excess mortality from liver cancer in the former poisonous gas factory workers. However, further investigation and statistical analyses including such confounding factors are required to establish the effect of MG exposure on the development of liver cancer.

Another noteworthy feature of this study is that the analyses included information about smoking status, the role of which cannot be ignored in the development of respiratory cancer and chronic bronchitis/emphysema. Despite close scrutiny of the medical records, we could collect only fragmented information about smoking status, which was limited to the presence or absence of smoking history. In the Cox proportional hazard analyses among male workers, 432 participants were excluded from the multivariate analysis for respiratory cancer mainly due to the lack of data on smoking history. Many participants with missing data (such as smoking history) had died during the early period after initiating our investigation of the health effects caused by MG. (The median year of death was 1972 for the 432 participants excluded from the analyses and 1988 for the entire cohort.) Considering the period of death, the causes of mortality in the workers excluded from the analysis may have been greatly affected by MG exposure and less affected by smoking. Thus, excluding the 432 workers from the analysis may have underestimated the risk of MG exposure on respiratory cancer mortality.

A potential explanation for the low SMRs for all-cause mortality in the 2392 male and 1226 female workers at the poisonous gas factory in Okuno-jima is the healthy worker effect. However, even when the healthy worker effect was taken into consideration, the SMRs for circulatory and digestive diseases appeared to be very low. This might be explained by the excessive number of deaths due to malignant neoplasms and respiratory diseases that would have thereby reduced the number of deaths due to other causes. Further, the workers received generous medical care including periodic health examinations and medical compensation, which might have partially contributed to the very low SMRs for circulatory and digestive diseases.

This study has a few limitations. First, the study cohort was restricted to the workers of the poisonous gas factory in Okuno-jima who had visited the Tadanoumi Hospital, mainly due to the difficulty in collecting personal information for workers who had attended other hospitals. In addition, there must be a concern regarding whether former workers who had visited the Tadanoumi Hospital were sicker than those who had not. However, we believe that the selection bias in this study cohort is unlikely for the following reasons: (1) the Japanese government urged all participants registered as former workers at the poisonous gas factory in Okuno-jima to attend medical institutions regularly by compensating them for their medical costs regardless of the severity of their health problems; thus, there were few non-hospital attendees among the former workers; (2) the majority of the former workers at the poisonous gas factory had visited the Tadanoumi Hospital, and all their medical records have been kept since 1952. Second, a significant number of former workers who had medical records at the Tadanoumi Hospital were lost to follow-up (177 males and 722 females) and thus were excluded from the final study cohort. However, we also found that there were not significant differences in the characteristics of the former workers between those lost to follow-up and the final study cohort (data not shown). Therefore, we believe that the exclusion of the individuals lost to follow-up from the final study cohort did not have a significant influence on the data analysis. Third, it is possible that the workers in Okuno-jima had been exposed both to MG and to arsenical agents, such as lewisite and diphenylcyanarsine, which are suggested to be carcinogenic. Because the vast majority of poisonous gas produced in Okuno-jima was MG, and only a small portion of the former workers dealt with arsenical agents, every former worker had a chance to be exposed to MG, but the exposure to arsenical agents was very limited. Therefore, the degree of exposure to MG could be roughly estimated by the job category that each former worker belonged to; however, there were no good methods for estimating the degree of exposure to chemical agents other than MG for each worker. Compared with MG, lewisite and diphenylcyanarsine were produced in much smaller quantities and are reportedly much less carcinogenic in humans.[6 24] Therefore, we excluded the effects of chemical agents other than MG in this study.

CONCLUSIONS

In this study, male workers of the poisonous gas factory in Okuno-jima exhibited significant excesses in mortality from cancers of the upper respiratory tract, stomach, liver and lung, as well as chronic bronchitis. Further, the analysis showed a causal relationship between mortality from upper respiratory cancer, lung cancer and chronic bronchitis/emphysema and MG exposure.

Applying the Okuno-jima MG Index, which integrated the mortality risk associated with job category in the factory and length of service, we found higher cumulative death rates for respiratory cancer and chronic bronchitis/emphysema in the group with a higher Okuno-jima MG Index. Therefore, the Okuno-jima MG Index may be a useful indicator for quantitatively estimating the cumulative extent of MG exposure.

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Contributors KM collected and analysed the data, and drafted and revised the paper. NH designed the study, monitored data collection and drafted and revised the paper. HI drafted and revised the paper. YO, YN and KK collected the data and drafted the paper. TA and JK designed the data analysis plan, analysed the data and revised the paper. NK designed the study and revised the paper.

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