



## Case Report

# Indolent B-Cell Lymphoid Malignancy in the Spleen of a Man Who Handled Benzene: Splenic Marginal Zone Lymphoma



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## ABSTRACT

We present the case of a 45-year-old man with a history of benzene exposure who developed splenic marginal zone lymphoma. For 6 years, he had worked in an enclosed space cleaning instruments with benzene. He was diagnosed with splenic marginal zone lymphoma 19 years after retirement. During his time of working in the laboratory in the 1980s, working environments were not monitored for hazardous materials. We indirectly estimated the cumulative level of past benzene exposure using job-exposure matrices and technical assumptions. Care must be taken in investigating the relevance of occupational benzene exposure in the occurrence of indolent B-cell lymphoma. Because of the long latency period and because occupational measurement data do not exist for the period during the patient's exposure, the epidemiological impact of benzene exposure may be underestimated.

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## 1. Introduction

Splenic marginal zone lymphoma (SMZL) is a B-cell lymphoid malignancy involving the spleen and other organs, which comprises less than 1% of all cases of non-Hodgkin lymphoma (NHL) [1]. Benzene affects nearly all blood cell types and is suspected to be toxic to progenitor cells [2]. Benzene has been designated as a carcinogen with limited evidence to cause NHL by the International Agency for Research on Cancer (IARC) [3]. It has been suggested that the effects of benzene on the human body decrease over time if there is no further exposure [4]. However, the latency period of NHL may be as long as 10 years [5]. The patient in our case study was exposed to benzene at work, and was diagnosed with SMZL 19 years after retirement. Because of the long latency period, direct data regarding the patient's past exposure did not exist. Therefore, we indirectly estimated the level of occupational exposure to benzene and confirmed the possibility of SMZL development secondary to benzene exposure.

## 2. Case Report

### 2.1. Current disease history

A 45-year-old man without a significant medical history was diagnosed with splenomegaly in August 2004. Bone marrow examination with immunohistochemical staining established the diagnosis of SMZL. The patient initially refused further treatment, but subsequently underwent splenectomy 7 months later. The patient completed chemotherapy and is continually observed.

### 2.2. Occupational history and working environment

For approximately 6 years, from December 1979 until October 1985, the patient was employed at the industrial standardization and calibration unit of the Testing Laboratory for Certification and Quality Evaluation. His job tasks included calibration of measuring instruments used in various fields. The patient cleaned evaluating

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machines to test the functionality of machinery parts and to support the certification of machinery products. The patient stated that he cleaned the machines using solvents such as benzene. The office was a tightly enclosed space, designed to maintain a constant temperature ( $20 \pm 0.2^\circ\text{C}$ ) and humidity level ( $55 \pm 0.52\%$ ). To reduce measurement error, air ventilation was not allowed and work was confined to the enclosed area. To remove oily dirt from measuring instruments, part surfaces were cleaned with a high concentration of benzene. Cleaning was performed repeatedly with bare hands and without personal safety equipment. The patient used a 500-mL bottle of benzene over 2 to 3 months, depending on the workload. After he left the job in 1985, no further exposure to agents known to affect the hematopoietic system was noted.

In the 1980s, working environments were not monitored for hazardous materials, and the patient's office was subsequently repurposed. Therefore, we estimated the level of benzene exposure by tracing the amount of benzene used in the past. According to job-exposure matrices developed by Park et al [6], who estimated past benzene exposure in the Republic of Korea based on past reports and measurement samples, the weighted arithmetic means for airborne benzene level between 1980 and 1984 was  $50.35 \pm 26.83$  ppm. Precision measurement is a relatively new field, and benzene exposure in the field cannot be directly compared to job-exposure matrices results. However, we believe that benzene was widely used in the past [6], and workers in diverse industries were exposed to high levels. We infer that our patient was also exposed to high levels of benzene. Second, we used assumptions regarding the patient's past working environment to estimate exposure. Based on the patient's statement that high-purity benzene was used, we assumed that 100% benzene was used to avoid underestimation of total exposure. There was one exit door in the room where the patient worked. Even if the door was not opened frequently, the level of total ventilation with a contaminating material in equilibrium was calculated using Equation 1 [7].

$$C = \frac{G}{\text{ACH} \times V} \quad (1)$$

where  $C$  is the concentration of contaminating material in the air (ppm),  $G$  is the generation rate of contamination (L/h), ACH denotes air changes per hour ( $\text{h}^{-1}$ ), and  $V$  denotes the volume of the room ( $\text{m}^3$ ).

Additionally, based on his statement regarding the volume of benzene used, we assumed a yearly use of 2,250 mL, and a daily use of 7.8 mL, considering 24 working days per month. Considering a daily use of 7.8 mL, the level of benzene evaporating into the air per day was estimated to be 6.8367 g/d ( $7.8 \text{ mL/d} \times 0.8765 \text{ g/mL}$ ). We used the molecular weight of 1 g of benzene (78.11 g/mol) and the standard volume (24.0 L) at a constant temperature of  $20^\circ\text{C}$  in order to determine 2.10 L of benzene evaporated daily. The volume of benzene that evaporates into the air (2.10 L) was divided by the volume of the workspace ( $4.8 \text{ m} \times 2.7 \text{ m} \times 2.5 \text{ m} = 32.4 \text{ m}^3$ ), the air changes per hour for an enclosed space with only one side having a window or exit door ( $0.67 \text{ h}^{-1}$ ) [8], converting 1 working day into 8 working hours, to ascertain the concentration of contaminating material in the air as 12.1 ppm. When applying exposure duration of 6 years, cumulative exposure level was extremely high at 72.6 ppm-years. The estimate was obtained based on extreme assumptions, and several environmental variables were not factored in. Despite this, it can be inferred that the patient was exposed to a high level of benzene while using high concentrations in an enclosed space. If the level of skin exposure to benzene is considered, based on the patient's statement that large quantities of benzene were touched during cleaning, the cumulative level of benzene exposure would be even higher.

### 3. Discussion

There is limited evidence regarding the IARC designation of benzene as a carcinogen causing NHL. Currently, an atypical effect of benzene metabolites on hematopoietic stem cells is thought to be the mechanism by which benzene causes cancer of the hematopoietic system [9]. An increased risk of NHL secondary to benzene exposure was shown in only five of 14 independent case-control studies between 1989 and 2010 [10]. However, the specific subtypes of NHL were not evaluated in these studies. Indolent NHL subtypes have a long latency period, and thus they are unlikely to have been fully accounted for in previous studies because they were not yet detectable, resulting in an underestimation of benzene's epidemiological impact [3].

Although the risk of leukemia is known to increase as the level of benzene exposure increases [11], some cohort and case-control studies have reported that the risk ratio of leukemia due to benzene exposure did not increase 20 years after the last exposure to benzene [4,12]. In contrast, one cannot conclude that the association between indolent NHL types and benzene exposure decreases over time after the last exposure, because of the long latency period until symptoms occur [11]. Therefore, care must be taken when investigating the occupational prevalence of benzene in the occurrence of indolent B-cell lymphoma. The long latency period after the last exposure does not imply that the likelihood of an occupational disease occurring decreases over time.

The trend of NHL occurrence due to benzene exposure is different from that of general NHL occurrence [13]. Of the 76 Korean cases determined to have a malignant lymphohematopoietic disease owing to benzene exposure from 1994 to 2012, nine patients had NHL, and the mean latency period from the exposure was  $17.2 \pm 7.3$  years, and the mean age at the time of diagnosis was  $44.8 \pm 7.6$  years [6,14]. Although there were only nine cases, these patients were diagnosed at a younger age compared to nonoccupational NHL patients, and there was a longer mean latency period after exposure to benzene. Similarly, the diagnosis in our patient was made at 45 years of age, and 19 years had passed since his last exposure to benzene.

We indirectly estimated the cumulative level of past benzene exposure using job-exposure matrices and technical assumption, and then we confirmed the possibility of SMZL development secondary to benzene exposure in this case report. There are many limitations in the estimation of the benzene exposure level for our patient as no occupational measurement data existed during the 1980s when our patient was exposed to benzene. Following termination of our patient's employment, the office was repurposed and we were unable to find an office with a similar environment in the literature. Thus, our estimate of benzene exposure is based on the patient's job type and self-reported benzene exposure. However, to ascertain the occupational relationship between benzene exposure and SMZL, the estimation of patient's previous exposure level is important. If there is no evidence for the calculation, we can infer the previous exposure level through the scientific methods. Accordingly, we estimated the exposure level by making extreme assumptions that the measurement room was an enclosed space, and all the benzene used would evaporate. We considered air changes per hour to derive a more accurate equation, but we did not consider many other variables with respect to loss owing to absorption and adsorption as well as chemical changes. Nonetheless, during the period when our patient worked, a high concentration of benzene was used. Hence, it can be concluded that he was exposed to a level of benzene that could cause an occupational cancer of the hematopoietic system.

SMZL, a rare indolent subtype of NHL, occurred in our patient with a history of exposure to high concentrations of benzene. There

were no other underlying risk factors predisposing this patient to SMZL, and the patient was younger than the typical patient with NHL. Our estimation measures for benzene exposure revealed that the patient was exposed to high concentrations of benzene. Therefore, it is reasonable to conclude that the patient developed an occupational indolent B-cell lymphoid malignancy owing to benzene exposure.

### Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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