Background

Multiple myeloma is a type of hematological malignancy known to arise from post-germinal center plasma cells (B cells) [1]. Multiple myeloma accounts for approximately 1% of all types of malignancies and 10%–15% of hematological malignancies [2]. Epidemiologically, the median age at diagnosis is 66 years with a less than a 15% prevalence among those younger than 50 [2,3]. Multiple myeloma is also known to occur more frequently in males and blacks [2,4]. In Korea, multiple myeloma accounts for 0.5% of all types of malignancies and 12% of hematological malignancies [5]. The crude incidence rate (per 100,000 person-years) of multiple myeloma in Korea was found to have increased from 1999 (1.0) to 2011 (2.1) [5].

Patients who suffer from multiple myeloma present with symptoms or signs related to the infiltration of plasma cells into the relevant body organs or renal damage from excessive proteins [6]. Major symptoms or signs at presentation are anemia, bone pain, elevated creatinine, generalized weakness, hypercalcemia, and/or weight loss [6]. A diagnosis of multiple myeloma is made when serum or urinary monoclonal protein and plasma cells in the bone marrow are present with accompanying end-organ damage [7]. Several epidemiological studies have suggested that occupational or environmental risk factors of multiple myeloma include ionizing radiation [8]; petrochemicals, and organic solvents such as benzene, heavy metals, asbestos, pesticides, and herbicides; however, the results are inconclusive [9,10]. Petrochemical, agricultural, wood, or printing workers as well as workers exposed to arsenic, lead, cutting oil, pesticides, or paints are believed to be at risk for developing multiple myeloma [11].

We present a case of multiple myeloma that occurred in a poultry farm worker who was exposed to pesticides and formaldehyde.

Case presentation

Patient

Sixty-one-year-old male.
Chief complaints
Generalized weakness and bone pain.

Past medical and family history
No specific past medical or family history.

Occupational history
No specific occupational history.

Present illness
The patient initially presented with bone pain accompanied by generalized weakness. The result of the urinalysis indicated signs of a urinary tract infection. Treatment with antibiotics was attempted, but without improvement. Thereafter, he was admitted for acute renal failure. Bone marrow biopsy was also performed, and the patient was diagnosed with multiple myeloma (IgG, lambda type, CRAB (−/+/+/+), ps1 iss3). Following the diagnosis, a hematologist started the patient on chemotherapy and hemodialysis.

Occupational site and job description
The patient was the sole operator of a poultry farm, established in 1996, that had three chicken sheds in operation from 1996 to 2005 and two from 2005. The measurement of each chicken shed was 105 × 8 × 3 meters with a maximum capacity of approximately 30,000 chickens. Aside from two air intake and exhaust ventilators, six ventilator fans are present on the sidewalls of each chicken shed. The air intake and exhaust systems are used during chicken rearing periods. After the chickens mature, they are shipped out of the sheds, and then a consecutive fumigation is performed (approximately 6 times/months). In order to maximize the fumigation effect, ventilators are only turned on after the fumigation is finished, regardless of whether a worker is present in the shed at the time of the fumigation.

Reenactment of the fumigation tasks were performed in January 2013 using personal samplers to estimate the levels of exposure to formaldehyde and organic solvents including benzene, which is an impurity sometimes present in pesticides (Figure 1). Samples were collected over the course of one hour. Eight-hour time weighted average exposure concentrations and the short-term exposure limit were calculated. The concentration of formaldehyde and benzene were estimated using NIOSH 2016 [12] and the 1501 methods [13]. Samples were analyzed using high-performance liquid chromatography for formaldehyde and gas chromatography with a flame ionization detector for benzene.

Table 1 Materials safety data sheet listing all products used in the poultry farm

| Product name        | Constituent          | CAS No. | Percentage |
|---------------------|----------------------|---------|------------|
| Formaldehyde        | Formaldehyde 35%     | 50-00-0 | 100        |
| DDVP                | Dichloro vinyl dimethyl phosphate | 62-73-7 | 90         |
| Olsozol             | Ortho-dichlorbenzene | 95-50-1 | N/S        |
| M-cresol            | Methyl alcohol       | 108-39-4 | N/S        |
| Gramoxone inteon    | Paraquat dichloride  | 1910-42-5 | 24       |
| Baroclean           | Benzaikonium chloride | 264-151-6 | 50        |
| Longlife            | High boiling tar acids | 84989-05-9 | 15 – 30   |
|                     | Chlorinated xyleneols | Mixture | N/S        |
|                     | Sulphonic acid       | 27176-870 | N/S       |

*Chemical abstracts service number.
N/S: Not specified.
The results of our analysis showed only small traces of benzene in the collected samples; however, our results may not be representative of the actual concentration of benzene in the pesticides used. The concentration of formaldehyde was estimated as 17.53 ppm, which greatly exceeds the time-weighted average and short-term exposure limit of 0.5 ppm and 1.0 ppm, respectively, that are suggested in the Korean Industrial Safety and Health Act (Table 2) [14].

Conclusions
Agricultural chemicals used in the fumigation tasks, including pesticides and formaldehyde, are suspected to be the main occupational risk factors in the current case. In 2011, 1,050 and 218,017 new cases of multiple myeloma and all types of malignancies were diagnosed in Korea, respectively [5]. Because of the rare nature of this disease, studies on the risk factors of multiple myeloma have not been able to provide conclusive evidence of potential occupational risk factors.

Considering the widespread use of agricultural chemicals such as pesticides and/or fungicides, agricultural workers, especially livestock breeders, are known to be at a high risk factor of developing hematopoietic cancer [15,16]. Poultry workers and agricultural farmers both use a substantial amount of agricultural chemicals and organic solvents for hygiene control [16,17].

The prevalence of multiple myeloma was higher among pesticide users than it was among other occupation groups according to the Agricultural Health Study (6.8% v. 3.7%, OR = 1.9, 95% CI: 1.3 2.7) [18]. In a case control study conducted in Canada, the risk of multiple myeloma increased when patients were exposed to carbamates or captan class fungicides (OR = 1.90, 95% CI: 1.11 3.27, 25 cases; OR = 2.35, 95% CI: 1.03-5.35, 14 cases) [19]. In another case control study from 2000 to

Table 2 Results of the exposure reenactment at the farm

| Organic solvent | Method | Time | TWA | STEL | Concentration (ppm) |
|-----------------|--------|------|-----|------|---------------------|
| Formaldehyde    | Personal | 13:30 to 14:30 | 0.5 | 1    | 17.53               |
| Benzene         | Personal | 13:30 to 14:30 | 1   | 5    | Trace               |

* Sampling method.  
* Sampling duration.  
* Time-weighted average suggested in the Korean Industrial Safety and Health Act.  
* Short-term exposure limit suggested in the Korean Industrial Safety and Health Act.
Among the different classes of agricultural chemicals, carbamates and organochlorides are known to be related to an increased risk of multiple myeloma [18,25]. Previous studies have not found a relationship between the occurrence of multiple myeloma and working with chickens [21,24]. Nevertheless, work environments can widely differ; therefore, the results of previous studies should be applied carefully [26].

Organic solvents such as benzene and formaldehyde, which our patient was exposed to, are both classified as group 1 carcinogens for hematopoietic cancer by the International Agency for Research on Cancer, and formaldehyde is a known risk factor for acute myeloblastic leukemia [27,28]. Formaldehyde has highly reactive properties and direct damage such as aberrations on peripheral blood cells or cytogenetic damage in bone marrow cells in animals have been observed [29]. After being absorbed into the body, most of the substance is converted into an oligomer in the form of a diol such as methanediol [30]. Since the molecular weights of oligomers are small enough to penetrate biological barriers [31], formaldehyde may also promote leukemogenesis by direct DNA damage and aneuploidy in hematopoietic stem or early progenitor cells [31-33].

Numerous previous studies have investigated the association between exposures to organic solvents and the occurrence of multiple myeloma. In a cohort study that included formaldehyde manufacturing factory workers, increased mortality was directly proportional to the peak exposure level, yet their results were not statistically significant (peak exposure <2.0 ppm, relative risk = 1.0, 11 cases; peak exposure 2.0 < 4.0 ppm relative risk = 1.65, 13 cases, 95% CI: 0.76 3.61, p trend >0.5; peak exposure ≥4.0 ppm, relative risk = 2.04, 21 cases, 95% CI: 1.01 4.12, p trend >0.5) [34]. Studies targeting embalmers and the occurrence of other hematopoietic malignancies including myeloid leukemia also suggested heavily exposed groups were at a high risk (OR = 3.9, 95% CI: 1.2 12.5 among embalmers who worked >34 years) [27]. Few studies have investigated the influence of benzene exposure. However, one cohort study found an increased risk for hematopoietic cancers including multiple myeloma among workers exposed to unrefined petroleum chemicals containing benzene as an impurity [35,36].

The patient in the present study had worked at the same poultry farm for the last 16 years and was in charge of managing consumable supplies and hygiene control. To maintain the hygiene of the chicken sheds, the patient performed fumigations with pesticides and formaldehyde, and ventilator fans were turned off during the fumigation process to enhance the efficiency of the fumigation. This lack of ventilation has likely led to excessive exposures to hazardous chemicals. In the reenactment of the patient’s fumigation process, levels of exposure to formaldehyde and benzene greatly exceeded the time-weighted average and short-term exposure limit suggested in the Korean Industrial Safety and Health Act [14].

As the results of the exposure reenactment indicates, the patient was repeatedly exposed to an extremely high level of formaldehyde and other agricultural chemicals including pesticides. Until now, a clear association between pesticides or formaldehyde exposure and an increased risk of multiple myeloma remain inconclusive; however, our patient’s exposure to formaldehyde was exceptionally high, thus potential risks cannot be neglected. In addition, considering the frequency and prolonged duration of exposure to these hazardous chemicals, the patient’s circumstance could be considered extraordinary. The patient presented with no other known risk factors for multiple myeloma; however, due to a lack of education on occupational safety measures, the patient wore no personal protective equipment while working.

Although this study lacks enough epidemiological evidence to establish an association with multiple myeloma, the rare nature of the disease and extremely high level of exposure to hazardous chemicals over a prolonged time leads us to believe that the patient’s multiple myeloma likely originated after occupational exposure. Most poultry workers in Korea are considered petty; therefore, exposure to numerous health hazards is common, and they tend to receive no proper education on protective measures. In the future, improvements to work environments and educational programs on occupational hygiene are required. Moreover, the health effects of agricultural chemicals should be further evaluated. Last, large-scale prospective studies tracking the concentrations of compound chemicals used in agricultural work are required, and techniques to reduce their health effects should be developed.

**Consent**

Written informed consent was obtained from the patient for the publication of this report and all accompanying images.
Additional file

Additional file 1: Table S1. Typical work schedule of the poultry farm.

Competing interests

The authors declared that they have no competing interests.

Authors contributions

PKI: The first author of this article. He designed this research, collected and interpreted the data, conducted reproduction of relevant tasks, prepared the draft of this manuscript, and approved the final version of the manuscript. IK: The corresponding author of this article. She designed this research, collected and interpreted the data, conducted reproduction of relevant tasks, prepared the draft of this manuscript, and approved the final version of the manuscript. IP: He reviewed materials safety data sheet, assessed exposure status of workplace, conducted reproduction of relevant tasks, revised the draft of this manuscript, and approved the final version of the manuscript. CK: He reviewed materials safety data sheet, assessed exposure status of workplace, conducted reproduction of relevant tasks, revised the draft of this manuscript, and approved the final version of the manuscript. EAK: She reviewed this design of this research, interpreted results, revised the draft of this manuscript, and approved the final version of the manuscript.

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