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Case Report

Chronic lymphocytic leukemia in a farmer and vegetable seller: Associated with exposure of multiple work-related hazards?

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Abstract

There are several risk factors associated with the incidence of chronic lymphocytic leukaemia (CLL), namely genetic factors, smoking, and occupational exposure to chemicals. We highlight a possible association of a CLL case and the occupational. We reported a case of CLL patient, a 69-year-old man, who had been working as a vegetable seller and a chili farmer since 15 and 4 years ago, respectively. The patient was diagnosed with CLL three months prior to admission and had a history of three times blood transfusions. The patient only complained of paleness and weakness without any specific symptoms. No swelling of the lymph nodes, hepatomegaly, or splenomegaly was found. As a vegetable seller and chili farmer, the patient was exposed to five hazards, physical, chemical, biological, ergonomic to psychosocial. Therefore, it is necessary to analyse whether there was an association between the patient's work and the current CLL. To diagnose occupational diseases, several steps are needed. In this patient, one of the risk factors that could lead to CLL was exposure to chemicals such as pesticides. However, information regarding the content of pesticides used was unclear and there were no results obtained from pesticides biomarker examination that might cause the disease, making it difficult to establish a definitive diagnosis of work-related cause. The patient could be advised to have biomarkers of pesticide substances checked, which requires control of farmers and vegetable sellers who might have been exposed to pesticides. The control mechanism might be started from elimination, substitution, engineering, administration, and use of personal protective equipment. A control mechanism is necessary to prevent the entry of contaminants into the body, especially through inhalation, oral, and dermal pathways. It is recommended to examine for biomarkers of pesticides containing organophosphates, organochlorines, or carbamates to determine the chronic effects on the accumulation of these chemicals that might cause CLL.

Keywords: Chronic lymphocytic leukaemia, farmer, vegetable seller, pesticide

Introduction

Chronic lymphocytic leukaemia (CLL) is a mature B-cell lymphoid neoplasm characterized by the accumulation of clonal populations of CD5+, CD19+ and CD23+ B lymphocytes in peripheral blood, bone marrow, lymph nodules, and/or spleen. Normally, the B lymphocytes go through cellular maturation within the bone marrow, starting in the form of hematopoietic stem cells and culminating into mature B cells. The mortality rate of CLL patients is 2 to 3 years on average after being diagnosed; however, many patients survive 5 to 10 years (Benavente et al., 2020; Muhammad, 2020; Nicholas et al., 2021).

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program had estimated that the number of CLL new cases in the US by 2018 was 20.940, with approximately 1.2% new cases, 4.510 deaths, or 0.7% cancer-associated deaths. The median age at diagnosis of CLL was 70 years with a peak between 65-74 years. The occurrence of CLL in the elderly is suspected due to the accumulation of toxins from chronic exposure. The incidence of CLL in men is up to twice as high as in women (Karakosta et al., 2016; Nicholas et al., 2021).

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In general, there are several risk factors for CLL, including a family history of cancer; exposure to radiation, pesticides, and smoking; living in an agricultural environment exposed to herbicides and pesticides; lack of sun exposure; medical history of atopy; exposure to hepatitis C virus; and infection. There is an increased risk in the industry and occupational exposures, especially to pesticides, agricultural agents, petroleum, rubber, wood care products, hair dyes, glues, and other solvents (e.g., benzene, butadiene), which can directly or indirectly lead to leukemogenesis mechanism that might be the pathogenesis of CLL. Exposure to pesticides, especially deltamethrin and herbicides, is associated with CLL (Hallek et al., 2018; Karakosta et al., 2016).

The risk of having CLL increases with a family history of leukaemia. Genome-wide association studies (GWASs) identified several polymorphic genetic loci in CLL cells where active transcription occurred, and contain genes responsible for controlling B cell development and signalling or immune function. The association between ionizing radiation and the incidence of CLL is still controversial since there was no increase in the number of cases in the Japanese population exposed to the atomic bomb during World War II. In contrast, studies on people in the vicinity of the Grenoble nuclear power plant breakdown suggested an increased incidence among exposed individuals (Hallek et al., 2018; Karakosta et al., 2016).

Studies regarding the effect of insecticides (endosulfan, methomyl, pyrethrin, and chlorpyrifos), herbicides (2,4D, atrazine, diquat, and diuron), and fungicides (captan and thiram) exposure on the incidence of CLL showed that the use of pesticides and individual active substances, as well as pyrethrin insecticides increased a cumulative exposure score (CES) up to more than 0.97. The weakest association was monitored among the insecticide methomyl. Furthermore, the duration of pesticide exposure showed a positive correlation with the prevalence, with the exposure intensity coefficient correlation of >0.71, suggesting an association between insecticide exposure and CLL. In short, occupational exposure to organic pesticides increased the risk of CLL, and the strongest association was observed in exposure to organophosphate insecticides. The results of this study were similar to that of a cohort study on farmers and pesticide users, which exhibited an association between exposure to pesticides, terbufos (organophosphate insecticide), as well as DDT (organochlorine insecticide) with a significant increase in the risk of CLL (Benavente et al., 2020).

Case report

A 69-year-old man came with complaints of weakness and paleness for 4 months prior to the visit. The patient had been hospitalized 3 times for blood transfusions. Three months ago, the patient was diagnosed with leukaemia upon a bone marrow examination and positive values acquisition of CD 20, CD 5, KAPPA, CD 43, CD 23 markers that led to CLL.

During this time, the patient worked as a fruit seller and chili farmer. In the morning, he usually traded in his own stalls selling vegetables, meat, fish and chicken. Meanwhile, in the afternoon, the patient went to the garden located around his house to plant chilies with his children. The patient had started farming since 2017 by planting chili seeds, sowing, watering and providing fertilizer. In addition, the patient also used pesticides and fungicides to deal with pests and fungi attacking the chili plants. The patient admitted that the application of pesticides and fungicides was erratic and did not use certain brands. Patients used fertilizer every 10-14 days.

While working as a vegetable seller and farmer, the patient was exposed to several potential hazards including physical (UV rays, noise, and inorganic dust), chemical (pesticides, insecticides and fungicides), and biological (bacteria, viruses and fungi, worms, insects or snakes). The patient was also exposed to ergonomic hazards which refer to awkward positions and repetitive movements that might cause back problems and moderate risk for wrists, neck and feet, as well as psychosocial hazards such as work-related stress that might occur while dealing with customers as seller and non-optimal harvests due to the drought.

Discussion

A proper analysis in the form of seven steps is needed to establish the diagnosis of occupational diseases. The patient reported in this case was diagnosed with CLL despite being asymptomatic, which usually occurs in 25-50% of CLL patients. The diagnosis was established through blood count, blood smear, and B lymphocyte immunophenotyping examinations, in which a clonal B cell population carrying the CD5 antigen and B cell markers was identified. The diagnosis of CLL was established upon the presence of B lymphocyte levels > 5000/microliter in peripheral blood for a duration of less than 3 months. Leukemic cells found in blood smears are typically small, mature lymphocytes with narrow cytoplasmic boundaries and dense nuclei that have less visible nucleolus and partially aggregated chromatin. These cells may be found mixed with larger or atypical cells, split cells, or prolymphocytes, which might make up to 55% of the blood lymphocytes. The discovery of prolymphocytes excessing this percentage would support the diagnosis of prolymphocytic leukaemia (B-cell PLL). Gumprecht nuclear shadows, or smudge cells found as cell debris, are other morphological characteristics found in CLL. CLL cells will express CD5 T cell antigens and B cell surface antigens CD19, CD20, and CD 23. Establishing a clinical diagnosis in this case was based on the results of bone marrow biopsy and examination of biomarkers in the blood, in which positive CD 20, CD 5, KAPPA, CD 43, CD 23 markers were found (Hallek, 2017).

The next step was to determine the potential hazards in this patient's working environment. There are several potential hazards assumingly associated with agricultural activities, including environmental hazards such as pesticides, synthetic fertilizers, diesel exhaust, ultraviolet radiation, biological dust, zoonotic viruses, and bacteria. In general, the patient had 5 potential hazards related to his work: physical, chemical, biological, ergonomic and psychosocial. The potential hazard that might be a risk factor for CLL among vegetable traders and chili farmers is chemical hazard, especially insecticides and/or fungicides which are commonly applied to vegetable and chili plants. The classification of insecticides include organophosphates, organochlorines, carbamates, and pyrethroids (Asghar et al., 2016; Curl et al., 2020).

Since the content of pesticides used by the patient is still unclear, it is difficult to establish the pathophysiology of pesticides-associated CLL in this patient. However, several references indicated that pesticides possessed potential carcinogenic effects, including CLL. In general, pesticides consist of herbicides (phenoxy acetic acid, phenoxy benzoic acid, thiocarbamates, triazines, anilids, dipyridyl compounds, phosphonates), insecticides (organophosphates, organochlorines, carbamates, pytheroids, rotenoids), fungicides (thiophthalimides, thiocarbamates, ethylene bis dithiocarbamates (EBDCs), and fumigants. The recommended use of pesticides is only for the pest eradication purpose and is not recommended to be utilized routinely; however, some farmers, including the patient in this study, used them in the wrong dose and mix since they did not undergo special training for pesticide use. Inappropriate use of pesticides might negatively affect the environment and human as they will pollute the air, water, and soil, affecting people working in agricultural areas and those who consume food containing pesticides. Frequent exposure to insecticides is associated with a higher risk than exposure to herbicides. Indoor pesticide exposure is also associated with a higher risk of leukaemia compared to the outdoor exposure (Alavanja et al., 2004; Pluth et al., 2019).

Several studies have shown the effect of pesticides on human's health. Pesticides have neurotoxin effects that might cause Alzheimer's and Parkinson's diseases, neuronal disorders and degenerative diseases, foetal defects and congenital anomalies, and cancer in humans. Fungicides and insecticides are also neurotoxins that have synapse modulating effects on neurotransmitters. An increased use of pesticides can increase the incidence of leukaemia, clone thyroid, brain, and several other types of cancer. Epidemiological studies indicated that many types of pesticides are carcinogenic, e.g., sulfallates, organochlorines, and sulphates. Meanwhile, other pesticides such as lindane and chlordane are suggested as the cause of tumours (Asghar et al., 2016).

Organophosphate studies in animals revealed a differential disorder of hematopoietic cells (parathion 4 mg/kg po) that induced weak clastogenicity in bone marrow cells. In vitro exposure to organophosphates in human bone marrow cells or CD 34+ in hematopoietic stem cells reduced progenitor capacity to differentiate and sever DNA double-stranded and MLL gene rearrangements. Organophosphates caused DNA damage (isophenphos), hypermethylation or tumour suppressor genes (diazinon), and chromosomal damage (phenithrothion) (Van et al., 2019).

Pesticides also cause leukaemia in children whose mothers were exposed to pesticide during pregnancy. Those who were exposed to permethrin, in particular, had seven times higher risk of developing leukaemia than those who were not. Permethrin is commonly used to protect pets from flea and to kill mosquitoes. These chemicals can change the activity of nervous system in insects, and are also considered carcinogenic in some studies. Leukaemia in children is caused by DNA changes during infancy. A research found that the time from pregnancy to 11 months of breastfeeding was critical for children, and a history of pesticides exposure during this period will give them twice the chance of developing leukaemia (Asghar et al., 2016).

In this case, the patient was diagnosed with CLL at the age of 69 years, whereas CLL is common in the elderly. This suggested that there was a genotoxic agents exposure accumulation in lymphoid or other tissues since the patient has worked as a vegetable seller and chili farmer for 15 and 4 years, respectively. Chronic accumulation of biologically active metabolites, especially in lymphoid, can react irreversibly to form DNA mutations and induce chromosomal aberrations, which are common in CLL, and might trigger mutagenesis and carcinogenesis (Karakosta et al., 2016).

Several pesticides including organochlorines (e.g., aldrin, chlordane, DDT, dieldrin), lead arsenate, creosote, and sulfallate have been proven to be carcinogenic in animal studies. Epidemiological studies showed an association between non-Hodgkin's lymphoma and the exposure to phenocyacetic acid, organophosphates, and organochlorines. Leukaemia is associated with the use of insecticides, carbamates, organochlorines, organophosphates, herbicides, and zoonotic viruses. A study by Boros and William suggested that exposure to leukemic cell lines (K562) was associated with increased dose of organophosphate insecticide (isofenphos) exposure in a dose-dependent leukemic cell proliferation (Alavanja et al., 2004).

To cause a carcinogenic effect, it is necessary to calculate pesticide exposure measurements including the duration of exposure or duration of work as a vegetable seller and farmer, the increase in harvest time or duration, and the use of specific chemicals (duration and frequency). This can be used as an assessment of the estimated exposure in the patient, as well as to determine the duration and intensity of exposure. Moreover, in this case, we suspected a low exposure to chemicals during his work as a vegetable trader and medium or high exposure during his work as a chili farmer. To determine the weight of exposure, questionnaires related to pesticide application, work practices, and use of protective equipment can be used. Although in this case, the patient admitted that he did not use certain brands of pesticides or certain ingredients, exposure to pesticides could increase the risk of health problems due to the patient's inappropriate use of personal protective equipment. The patient did not use special personal protective equipment while working, such as particular clothes, and did not wash his hands or clean them after work (Alavanja et al., 2004).

Several studies showed the association of pesticides with cancer, especially prostate cancer, non-Hodgkin lymphoma, leukaemia, multiple myeloma, bladder cancer, and colon cancer. The pesticides associated with leukaemia usually contains thiocarbamate and organophosphate with a relative risk of 2.36 (1.16-4.84) and 2.38 (1.35-4.21). In addition, the content of pesticides containing chlorinate phenol, triazine, pyrethroid were also associated with the risk of leukaemia, which increased the farmers' risk of developing cancer (OR=1.459, 95% CI 1.229-1.731) compared to non-farmers. Apart from farmers, the common household use of pesticides is pyrethroid. This insecticide was associated with haematological cancer, especially leukaemia. The most common exposure to the human body was through the oral and skin route. After entering the organism, pyrethroids will undergo metabolism and elimination. In mammals, pyrethroids are rapidly metabolized and eliminated through the urine and faeces several days after exposure. Permethrin reaches peak concentrations hours after oral exposure in blood plasma and is eliminated within 48 hours through the urine. The pyrethroid metabolic pathway is via ester hydrolysis and oxidation, which is mediated by carbocyl esterase and cytochrome P450. Although pyrethroids are eliminated faster than other pesticides, chronic exposure might lead to the development of cancers (Curl et al., 2020; Navarrete-Meneses and Perez-Vera, 2019).

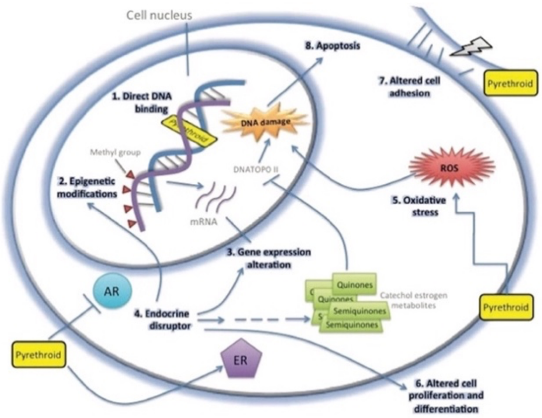

Figure 1. The process of DNA damage due to pyrethroids (Navarrete-Meneses and Perez-Vera, 2019).

For pesticides to develop into cancer, it also needs other environmental factors such as smoking, alcohol, and ultraviolet radiation. The development of cancer can occur due to DNA damage as shown in Figure 1, where pyrethroids bind directly to DNA causing DNA methylation. This can change the expression of genes that interfere with oestrogen and androgen receptors, which cause DNA damage and induce apoptosis. Pyrethroids also have endocrine disruptor effects that act as agonists or antagonists of oestrogen, androgen, and thyroid hormone receptors. In general, pesticides cause DNA damage, oxidative stress, metabolic output, and related thyroid effects in humans (Curl et al., 2020; Navarrete-Meneses and Perez-Vera, 2019).

Conclusion

Establishing a work-related diagnosis requires further investigation and examination, especially that related to pesticide biomarkers examination. One of the factors that might help establish the cause of pesticides-associated CLL is the cumulative dose response without determining the duration of chronic exposure, which might cause chronic effects including cancer development. For this reason, further occupational management is needed regarding the control that can be carried out by this patient during work as he return to work, both as a vegetable seller and a farmer.

Authors' contributions

Conceptualization: DSS and FR; Data curation: DSS and FR; Formal analysis: DSS and FR; Investigation: DSS; Methodology: DSS and FR; Resources: DSS and FR; Supervision: FR; Validation: FR; Writing-original draft preparation: DSS; Writing-review and editing: DSS and FR.

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Conflict of interest

There is no conflict of interest was reported by the authors.

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