CLINICAL RESEARCH

Is Occupational Arsenic Exposure a Possible Causative Agent of Breast Cancer for a Young Female Laboratory Technician? A Case-Study

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ABSTRACT

A 28-year-old female laboratory technologist who was exposed to highly concentrated inorganic arsenic for 7 years, 25 hours a week, presented with left breast cancer. When most epidemiologic evidence reported by the International Agency for Research on Cancer (IARC) supported the relationship between arsenic exposure and cancers of lung, skin and bladder; literature had documented increased risk of breast cancer in specific populational subgroups due to the estrogen-like activity of arsenic. The existing available control measures are restricted to the administrative control such as training and job rotation, hence making the causal assessment of occupational cancer is challenging due to the lack of relevant data on the worker's biological monitoring and environmental exposure monitoring data, together with the insufficient genetic composition information like Breast Cancer Genes1 (BRCA1). Moreover, the poor work practice and hygiene had made the exposure through dermal contact and digestion possible. The interpretation of work causal relationship while distinct occupational cancer from those of non-occupational must consider individual susceptibility as low-level short-period exposure might increase the risk for certain worker. Therefore, a systematically collected medical surveillance data along with industry hygiene data is highly recommended in order to assist in the refinement of human dose-response relationship of specific work carcinogen

Keywords Occupational Exposure - Arsenic - Causative Agent - Breast Cancer.

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INTRODUCTION

Arsenic has long been recognised as carcinogen by the IARC. Its causal relationship with breast cancer is under ongoing investigation.[1] Carcinogenesis is complex; The inherited factor interacts with environmental carcinogen exposure. Occupational exposure reported attributed to 5% of cancer development.[2] In this report, we focus on the chronology of breast cancer development following occupational arsenic exposure.

CASE PRESENTATION

A 28-year-old female who has been working for 7 years since 2009 as the medical laboratory technician in a research laboratory, presented with 2 weeks history of single left breast lump measuring 3cm during breast self-examination in February 2017. Upon examination under biopsy in March 2017, the mass was graded pathologically as Breast Carcinoma in Situ ($T_{is}N_0M_0$). Subsequent CT scan thorax, abdomen and pelvis reported no evidence of distance metastasis. The worker has undergone wide local excision of left breast lump in April 2017 and the operative finding was reported as Grade 3 invasive breast carcinoma with clear margin ($T_2N_1M_x$), hence followed by left axillary clearance a month later which revealed 2 out of 27 lymph nodes were positive for malignancy.

Gynaecological and family history

She was para 2 in 2017, with last child birth in 2015. She practiced breast feeding for both children up to 1 year old, never on hormonal contraception or drugs and had normal menstrual history. There is none of her first degree or second-degree relatives with family history of breast lump. The BRCA gene screening is not a routine clinical practice therefore the genetic status was unknown.

Employment history, work activity and occupational exposure

This was her first employment. She started working as a medical laboratory technician in the similar work unit since 2009, and full time handling the similar work procedure where she had direct exposure to multiple chemicals, namely arsenic trioxide, ceric ammonium sulphate, ammonium persulphate, sodium chloride, potassium iodate. She worked from 8.00a.m until 5.00p.m daily for five days a week, without shift rotation. Her main task was weighing the arsenic trioxide powder of 5-10grams each time (exposure duration of 2-3 hours per day, as frequent as 5 days in a week), and next to dissolve the arsenic powder in beaker and transport the beaker to another laboratory which is 5 meters away. In the second laboratory, she involved in the reagent preparation using all chemicals and lastly pipette the reagents into urinary sample. This entire work process took 2 hours. The worker put on dust mask, nitrile glove, gown and shoe cover while working in laboratory. Upon further interview regarding the Occupational Safety and Health measure, the worker had been given briefing on the relevant Safety Data Sheet (SDS) of all chemicals handled, and was provided with chemical handling training 2 yearly. She performed the similar laboratory tasks with another co-worker who was a 27-year-old male technician, well without ill-health complain. The arsenic trioxide powder weighing procedure was supposed to be performed in the enclosed fume hood however this standard operating procedure could not be adhered to from October 2012 until June 2016 due to the fire incident that occurred in her laboratory. For that 44 month, her work unit had been temporarily transferred to another workstation without the standardized laboratory setting, as well as without partition between the working bench and the rest/eat area. Being involved in the similar task with same magnitude of exposure to all chemicals, she was performing the arsenic powder weighing procedure in opened bench rather than fume hood, and next transferred the diluted arsenic with hand trolley to another laboratory which was located in separate building, 50 meters away from her original workplace. She denied of single incident of accidental chemical exposure and the occupational hygiene survey and health risk assessment were not conducted in her temporary work station from 2012-2016. The workplace medical surveillance program was initiated since 2016. The biological effect monitoring for liver, renal, haematological system were normal; while no biological monitoring of blood/ urine arsenic was conducted.

Non occupational risk factors of cancers

With the BMI of 30.4, she was categorized as obese Class I, had sedentary lifestyle but denied of exposure to other carcinogenic agents such as ionizing radiation, or breast cancer induced chemicals like diethylstilbesterol and polycyclic aromatic hydrocarbon. She had not been working during night shifts, non-smoker, has no comorbidities or positive family history of cancer.

DISCUSSION

Occupational cancer is cancer that is caused wholly or partly by the exposure to at least one cancer-inducing agents in the workplace The diagnosis of occupational cancer is always a challenge as in many cases the causal effect relationship between site of cancer possible work agents might not be straightforward. Furthermore, the occupational and non-occupational cancer are not differed substantially clinically or pathologically.[3] Koh and Seng (2001) had highlighted several criteria to be used as a guide on occupational cancer diagnosis, including the cancer clusters in the workplace of similar exposure, rare type of cancer, the positive link between suspected cancer-causing agents and

specific site of resulting cancer, typical latent period of 10-15 years or longer as well as the absence of non-occupational risk factors.[2]

Epidemiologically, the incidence rate of breast cancer increases with age, from 1.5 cases per 100,000 in women of 20-24 years of age to a peak of 421.3 cases per 100,000 in women of 75-79 years of age. It has been reported that 95% of the new cases occur among women aged 40 years or older; with the median age of women at the time of breast cancer diagnosis at 62 years.[4] Given that breast cancer is the most common cancer (33.9%) among the Malaysian women based on Malaysian National Cancer Registry Report 2016, typically, younger women have lower risk of getting breast cancer as epidemiological data reported only 5% of those aged 40 and below will be diagnosed with the disease; however, in present case, the worker presented with breast cancer at age of 28. Cancer cluster at the similar workplace did not generate meaningful information as she had only one male co-worker. The underlying causes of cancer are multiple, complex and interacting with one another. The inherited genetic factor will interact with lifestyle (nutrition, social and personal habit) as well as the environmental exposure including those carcinogens exposed during work. The occupational exposure has been reported attribute to up to 5% of the cancer development.[2]

Breast cancer has a strong familial component where the genetic factor plays the most crucial role in predicting the cancer risk. Nevertheless, the cancer risk prediction models are often too complex, require continuous validation employing latest database from local population in order to ensure its applicability in the setting it will be used. The prediction model or breast cancer risk assessment tool will not be accurate without the complete information on genetic component especially the mutation of the *BRCA1* or *BRCA2* gene.[5]

The establishment of work exposure is needed to determine the diagnosis. Among the list of chemical agents that she had a contact with, the highly toxic inorganic form of Arsenic Trioxide falls under the Group 1 carcinogen which is a known carcinogen to human. It is associated with several adverse effects dependent on dose, duration and exposure frequency. The common cancer sites reported linked to chronic inorganic arsenic exposure are the skin, bladder, lung, liver, kidney and prostate cancer, based on sufficient evidence in human study.[6] Moreover, the genotoxic role of the inorganic arsenic has been reported with its ability to alter the genetic composition of targeted calls, resulting in DNA modifications such as aneuploidy, micronuclei formation, chromosomal aberrations, deletion mutations, sister chromatid exchange and DNA-protein cross-linking,[7] supported by its genotoxic mechanism in inducing oxidative stress and altered patterns of DNA repair.[8] The inhalation has been demonstrated as the primary route of occupational exposure in various work setting, however, in this case the route of entry from ingestion and dermal exposure cannot be ruled out due to poor work practice or hygiene where worker perform weighing of arsenic powder in opened air rather than the use of fume hood.

The causal effect relationship between the arsenic exposure and breast cancer has not been reported by the IARC, however, the ongoing systematic evaluation on carcinogenicity of arsenic and the type of cancers that it may cause are still under investigation.[9] Khanjani and colleagues had concluded in the systematic review of epidemiological studies that arsenic was reported increase breast cancer risk in 4 out of 7 studies via the measurement of arsenic concentration in subjects' tissue.[10-13] The review provided evidence that genes and individual metabolic variations can play an effective role in arsenic carcinogenesis. The arsenic is metabolized in the human body by a chain of reduction and methylation reactions, in which Pentavalent arsenic (MMAV) is reduced to trivalent arsenic (MMAIII) and next turns into monomethylarsonic acid MMA, dimethylarsinic acid DMA and trimethylarsinic acid TMA by methylation reactions that decrease the toxicity of arsenic in the body and are eventually excreted in the urine. The arsenic methylation is varying between women of different individual susceptibility, hence result in intra-individual variation of breast cancer development.[11] Arsenic has long been recognized as a potent carcinogen at high concentrations. In a Polish study, women whose blood levels of arsenic were in the highest quartile had a 13-fold increased risk of developing breast cancer, compared to women in the lowest quartile; which suggested that blood arsenic level may be a useful predictive marker of cancer risk in women, especially those who are BRCA1 mutation carriers.[14, 15] In females, arsenic may influence the development of breast cancers by disrupting the function of estrogen receptors and suppressing the signalling pathway of estrogen, leading to the proliferation of cells in an estrogen-responsive breast cancer cell line.[16] In our case, there is the lack of relevant data on the worker's biological monitoring of arsenic level within body, and the exposure monitoring data on the work environment's arsenic concentration. On the other hand, the insufficient genetic composition information making the causation assessment a huge challenge. Although data regarding human carcinogenicity from chemical carcinogen uniformly implicate high-dose exposure, this cannot be practiced at all time. The conclusion of occupational cancer always taking into account the individual susceptibility as low-level short-period exposure may increase the risk for certain worker.

Workplace management

The European Commission of Information notices on diagnosis of occupational diseases highlighted a minimum intensity of exposure needed for inorganic arsenic to cause malignancy when occupational exposure is confirmed, need to conduct further assessment of working conditions which provides evidence of prolonged exposure to heavy arsenic dust or vapour content; and, if available, the biological monitoring along with workplace air monitoring data. On the other hand, the minimum duration of exposure for arsenic to cause malignancy is documented as 1 year with the induction period of five years. The worker in present case spent around 5 hours a day, 25 hours a week for 7 seven years of exposure to inorganic arsenic at work. Although the amount of exposure was minimal but the due to the highly concentrated arsenic trioxide, poor hygiene and poor work practice, route of entry via dermal or ingestion cannot be excluded. The control measures were inadequate such as no local exhaust ventilation, inappropriate respiratory protection as worker was using dust mask rather than chemical filtered respirator, inadequate training and supervision, inadequate medical surveillance program. Therefore, it is recommended that a systematically collected medical surveillance data together with industry hygiene data on exposure monitoring could help in the refinement of human dose-response relationship of specific work carcinogen.

Carcinogenesis is a multistage process involving the carcinogen induced genetic damage in susceptible cells, the activate proto-oncogenes and deletion of tumour suppressor gene, finally followed by the clonal expansion. Majority of the carcinogens have both initiating and promoting capability therefore a single mutation in a single cell is able to cause malignancy and there should not be any "safe level" for carcinogens, especially the genotoxic carcinogen.[2] The latency period which is defined as the period between first exposure and first clinical symptoms correspond with the carcinogenesis stages. Screening or surveillance for high-risk workers must be done after the initiation stage but before the development of clinical disease.

The workplace exposures of known or suspected carcinogens based on IARC guide are preventable and can be minimized. Adhering to the hierarchy of control, carcinogen need to be identified during the stage of chemical purchase to avoid introducing carcinogen into workplace. It is important for the regulatory enforcer and organizational management to advocate for measurable and continuous reduction of exposures caused by work in order to eliminate occupational cancer.[17] On the other hand, substitution of known carcinogenic, mutagenic and repro-toxic substances must be prioritized. Furthermore, workers' protection can be enhanced via the engineering control like provision of local exhaust ventilation, administrative control (hazard communication through training, information, instruction, supervision, hygienic work practice, job rotation, facilities for showering, washing and changing, exposure monitoring, medical surveillance program and education) together with the appropriate personal protective equipment as guided in the chemical safety data sheets.[18] The establishment of workplace registry is of paramount importance in order to record the workforce exposed to occupational carcinogens and the relevant information on work environment and workers in order to allow better environmental and personal monitoring program, health education and research efforts. Moreover, occupational cancer can be effectively controlled via the workplace policy, quantitative risk assessment, exposure limit control below the permissible exposure limit as well as the implementation of control measures take into account chemical volatility or the potential for skin absorption other than the typical inhalation route of exposure.

CONCLUSION

Although most of the epidemiologic evidence surrounding arsenic exposure has reported in terms of an increased risk of cancers at targeted organs of the lung, skin and bladder. The exposure to arsenic has been reported link to the increased risk of breast cancer in specific populational subgroups, depending on individual susceptibility, magnitude of arsenic exposure and the in-body metabolism; and low-level short-period exposure may increase the risk. The occupational breast cancer secondary to arsenic exposure in the work setting where control measures were inadequate, is possible. Therefore, a good workplace exposure reporting and record keeping of each worker exposed to the known human carcinogen might provide a helpful clue to distinct between occupational and non-occupational cancer and guide the causal assessment in the future.

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REFERENCES

1. Palma-Lara I, Martínez-Castillo M, Quintana-Pérez J, et al. Arsenic exposure: A public health problem leading to several cancers. *Regulatory Toxicology and Pharmacology*. 2020;110:104539.
2. Koh D, Seng CK. *Textbook of occupational medicine practice*: World Scientific; 2001.
3. Hamano G, Kubo S, Takemura S, et al. Comparison of clinicopathological characteristics between patients with occupational and non-occupational

intrahepatic cholangiocarcinoma. *Journal of Hepato-Biliary-Pancreatic Sciences.* 2016;23(7):389-396.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: a cancer journal for clinicians.* 2019;69(1):7-34.
5. Cintolo-Gonzalez JA, Braun D, Blackford AL, et al. Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. *Breast cancer research and treatment.* 2017;164:263-284.
6. Humans IWGotEoCRt. Arsenic and arsenic compounds. *Arsenic, Metals, Fibres and Dusts*: International Agency for Research on Cancer; 2012.
7. Faita F, Cori L, Bianchi F, Andreassi MG. Arsenic-induced genotoxicity and genetic susceptibility to arsenic-related pathologies. *International journal of environmental research and public health.* 2013;10(4):1527-1546.
8. Martinez VD, Vucic EA, Adonis M, Gil L, Lam WL. Arsenic biotransformation as a cancer promoting factor by inducing DNA damage and disruption of repair mechanisms. *Molecular biology international.* 2011;2011.
9. Khanjani N, Jafarnejad A-B, Tavakkoli L. Arsenic and breast cancer: a systematic review of epidemiologic studies. *Reviews on environmental health.* 2017;32(3):267-277.
10. Baastrup R, Sørensen M, Balstrøm T, et al. Arsenic in drinking-water and risk for cancer in Denmark. *Environmental health perspectives.* 2008;116(2):231-237.
11. López-Carrillo L, Hernández-Ramírez RU, Gandolfi AJ, Ornelas-Aguirre JM, Torres-Sánchez L, Cebrian ME. Arsenic methylation capacity is associated with breast cancer in northern Mexico. *Toxicology and applied pharmacology.* 2014;280(1):53-59.
12. Muszyńska M, Jaworska-Bieniek K, Durda K, et al. Arsenic (As) and breast cancer risk. *Hereditary Cancer in Clinical Practice.* 2012;10:1-1.
13. Pineda-Belmontes CP, Hernández-Ramírez RU, Hernández-Alcaraz C, Cebrián ME, López-Carrillo L. Genetic polymorphisms of PPAR gamma, arsenic methylation capacity and breast cancer risk in Mexican women. *salud pública de méxico.* 2016;58:220-227.
14. Marciniak W, Derkacz R, Muszyńska M, et al. Blood arsenic levels and the risk of familial breast cancer in Poland. *International journal of cancer.* 2020;146(10):2721-2727.
15. Marciniak W, Matoušek T, Domchek S, et al. Blood Arsenic Levels as a Marker of Breast Cancer Risk among BRCA1 Carriers. *Cancers.* 2021;13(13):3345.
16. Chatterjee A, Chatterji U. Arsenic abrogates the estrogen-signaling pathway in the rat uterus. *Reproductive Biology and Endocrinology.* 2010;8:1-11.
17. Musu T, Vogel L. Cancer and work: understanding occupational cancers and taking action to eliminate them. 2018.
18. Keefe AR, Demers PA, Neis B, et al. A scoping review to identify strategies that work to prevent four important occupational diseases. *American Journal of Industrial Medicine.* 2020;63(6):490-516.