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Review Article

Dermatological manifestations of arsenic exposure

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ABSTRACT

Arsenic is a toxic metal which is found ubiquitous in nature. The past decade has witnessed a significant increase in global arsenic contamination with reports of arsenic-induced toxicity from several regions. Arsenic exposure can be from natural, industrial, or medicinal sources. Of this, natural groundwater contamination tops the list. Arsenic in toxic doses can cause both acute and chronic ill effects on the human body. Cutaneous and neurological changes are the earliest and the most common manifestations of chronic arsenic toxicity and hence provide a clue to early diagnosis. Dermatological manifestations may be the presenting symptom and include pigmentary changes, nail manifestations, arsenic keratosis, changes affecting distal extremities, and cutaneous malignancies. There is no established specific treatment for arsenic toxicity, though chelating agents have been tried with varying results.

Keywords: Arsenic, Contamination, Groundwater, Toxicity, Manifestations

INTRODUCTION

Nearly 230 million individuals from over 108 countries across the globe are currently at risk of arsenic toxicity.[1] The World Health Organization (WHO) defined "arsenicosis" as a "chronic health condition arising from prolonged ingestion (not less than 6 months) of arsenic above a safe dose, usually manifested by characteristic skin lesions, with or without involvement of internal organs."[2] With the reported rise in global prevalence of arsenic toxicity, it becomes important for health-care professionals to be aware of the various sources of exposure to arsenic, effects of arsenic on various organs, and the available treatment options.

Dermatologists have a crucial role to play in the early diagnosis of arsenic toxicity, since many a time, the initial manifestations are cutaneous. At present, no accepted international guidelines are available for the diagnosis and management of arsenicosis.[3] In this review, we have tried to give an overview on arsenic toxicity with special reference to dermatologic manifestations.

ARSENIC

The term "arsenic" came from the Latin word "arsenicum" which was adopted originally from the Syriac word "(al) zarniqa," meaning "yellow orpiment."[4] Earlier it was considered as a metalloid because of its combined metallic and non-metallic characteristics, but currently in the context of toxicology, it is considered as a toxic metal, which is colorless, tasteless, and odorless.[5] In nature as well as within the human body, arsenic can combine with other elements such as iron, sulfur, chlorine, and oxygen to form inorganic arsenic and with hydrogen and carbon to form organic arsenic.[5] Organic form known as arsenobetaine is the least toxic form of arsenic, which is

commonly found in sea food, poultry, mushrooms, and rice. Inorganic forms are the toxic contaminants of groundwater and medicinal preparations.[5] Inorganic forms can exist in trivalent (arsenite) or pentavalent (arsenate) state. The trivalent form (arsenite) is more toxic than the pentavalent type.[5]

Arsenic is metabolized in the liver and detoxified by conversion into monomethylarsonic acid and dimethylarsinic acid.[3,5] Excretion is mainly through the kidneys (90–95%).[6]

SOURCES OF EXPOSURE

The main sources of arsenic exposure are natural, industrial, and medicinal. It can enter the human body through inhalation, ingestion, or percutaneous absorption.

The natural sources of arsenic contamination include rocks, soil, and natural water, of which the most common is groundwater. In India, high arsenic levels were reported in shallow alluvial aquifers whereas deep aquifers (>200 m) are considered safe.[7] Other sources include coal power plants, burning of vegetation, and volcanic eruptions.

Arsenic can also be found in the manufacturing industry in wood preservatives, herbicides, pesticides, insecticides, fungicides, paints, high emitting diodes, and semiconductors.[8] Researchers have shown that burning of chromium copper arsenate (CCA)-treated wood (used in building of decks and playgrounds) can release toxic levels of arsenic; hence, CCA-treated wood is now banned in Europe, Asia, and the United States of America (US).[9-11] Microchips which were initially made from silicon substrates are increasingly being replaced by gallium arsenide and arsine.[12] It has been recommended that quantity of arsenic in cosmetic preparations should be less than 5 ppm (parts per million). Studies have shown that color pigments used in eye shadows contain arsenic, which can cause eyelid dermatitis and even cancers on long-term use.[5]

Earlier, arsenic was widely used in various medicinal preparations such as Fowler's solution ($KAsO_2$), Donovan's solution (AsI_3), Asiatic pills (As_2O_3), and as an aphrodisiac along with opium. It was an ingredient of various herbal preparations as well.[13] Arsenic preparations were used in the treatment of various diseases such as asthma, chorea, psoriasis, pemphigus, eczema, leukemia, pernicious anemia, and Hodgkin's disease and empirically for syphilis, leprosy, and yaws.[3] Siefring *et al*., reported a patient who developed multiple squamous cell carcinomas (SCCs) following long-term ingestion of arsenic-containing traditional medicines for chronic plaque psoriasis.[14]

GLOBAL BURDEN

The South and Southeast Asian countries such as India, Bangladesh, Nepal, and China account for the highly arsenic polluted areas of the world. These areas are affected due to the arsenic-rich sediments deposited in the Brahmaputra-Gangetic river basin which was formed millions of years ago.[15]

INDIAN SCENARIO

In India, over 50 million people residing in 21 states and four union territories have so far been affected by arsenic contamination in groundwater [Figure 1].[1,15]

RISK FACTORS

Men are at a higher risk for arsenic-induced skin changes than women. This is attributed to the more efficient metabolism of arsenic in women through methylation. Other risk factors for arsenic poisoning are increasing age, smoking, sun exposure, folate deficiency, hyperhomocysteinemia, elevated serum creatinine levels, and genetic variability in arsenic metabolism.[16]

MECHANISM OF TOXICITY

Arsenic (As^{3+}) binds to sulfhydryl groups in keratin filament and accumulates in skin, hair, nails, and mucosae.[3] It then alters the levels of various growth factors, cytokeratins and transcription factors that affect the differentiation and proliferation of keratinocytes. Arsenic upregulates interleukin (IL)-1, IL-8, granulocyte macrophage colony-stimulating factor, transforming growth factor-β, tumor necrosis factor-α, and keratin–8, 16, and 18 and decreases the expression of transcription factors activator protein AP-1 and AP-2, loricrin, filaggrin, small proline-rich (spr) protein1, and keratin 10.[17]

Methylation of trivalent arsenic within the body (earlier considered a detoxification process) is now regarded as a cause for carcinogenesis.[18] Chromosomal abnormalities, oxidative stress, altered deoxyribonucleic acid (DNA) repair, p53 gene suppression, altered DNA methylation patterns, and gene amplification are the proposed mechanisms through which arsenic induces carcinogenesis.[16] According to recent study, arsenic upregulates aquaporin 3 expression, leading to autophagy of keratinocytes, thus promoting carcinogenesis.[19]

DERMATOLOGICAL MANIFESTATIONS

Six months to 2 years or more of continuous arsenic exposure is the average time period before the appearance of cutaneous manifestations.[6]

Dermatological manifestations of chronic arsenic toxicity

Pigmentary changes

Pigmentary changes are the earliest cutaneous changes [Figures 2 and 3] of chronic arsenic toxicity. The various

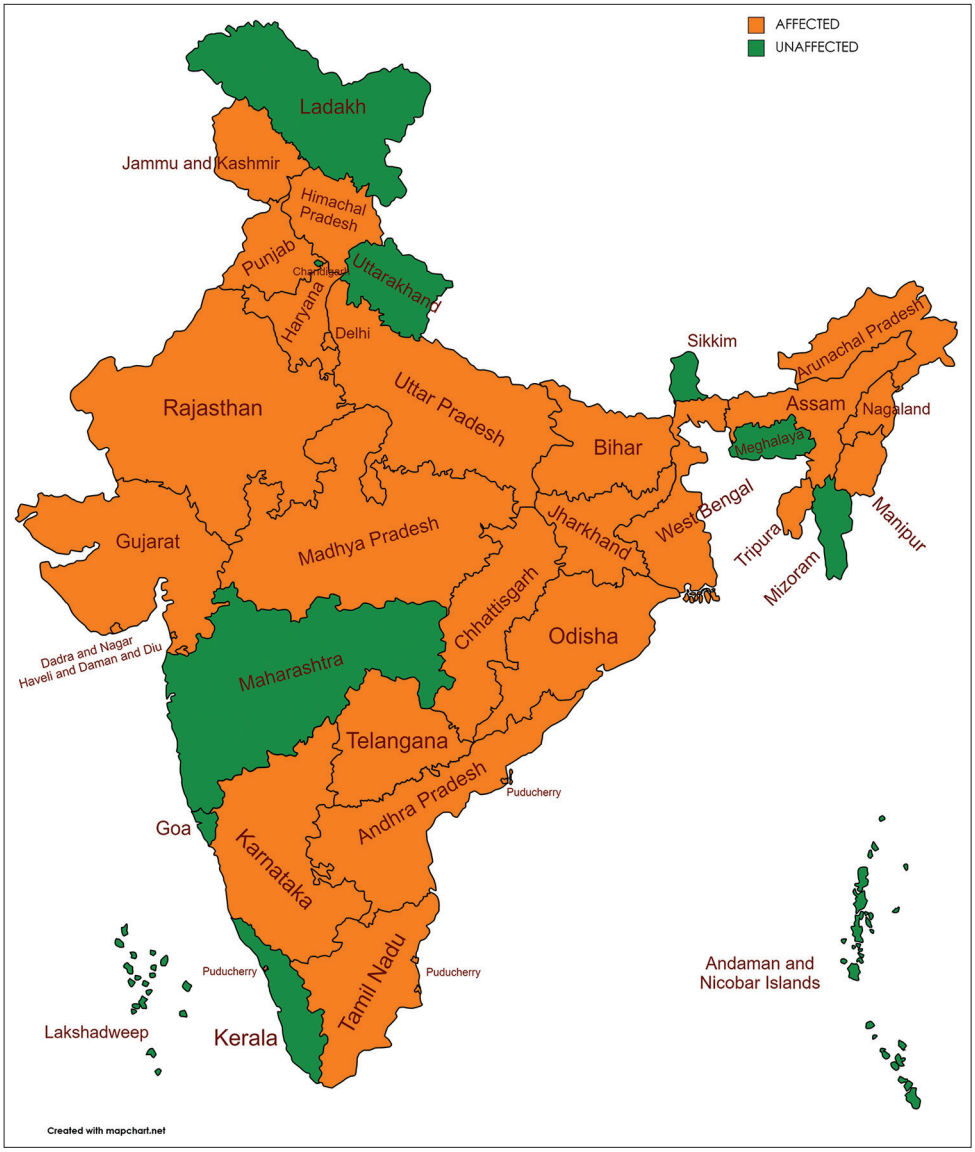

Figure 1: States harboring areas endemic for chronic arsenicosis.

patterns described are diffuse melanosis, spotted melanosis or freckled raindrop pattern, leukomelanosis, dyschromia, and mucosal pigmentation. The common sites affected are the nipples, axilla, groin, palms, soles, and pressure points, but may later extend to other parts of the body.[20]

Diffuse melanosis

Diffuse hyperpigmentation is usually seen in the palms and soles. It can involve any part of the body, but is most common over the sun protected sites.[18]

Spotted melanosis or raindrop pigmentation

It usually appears on the chest, back of trunk, and limbs as spotty hyperpigmentation [Figure 2] like that of "rain drops on a dusty road."[21] In a study conducted in Kolkata in 1994, raindrop pigmentation was the most common cutaneous change seen in 71% of total 110 patients with suspected arsenicosis.[22]

Leukomelanosis

These are depigmented macules appearing on the normal skin or on a hyperpigmented background and are seen in about 1/3rd of the patients. It appears in the advanced stage of the disease or in those who have stopped drinking arsenic-contaminated water, but had presented with spotted melanosis in the early stages. This was first observed by Saha *et al.*, who attributed it to destruction of melanocytes in the later stages.[21]

Dyschromia

Dyschromia refers to the simultaneous appearance of hyper and hypopigmented macules. In advanced disease, this may involve large areas of the body and even appear as xerodermoid.[18]

Mucosal pigmentation

It presents as diffuse or blotchy pigmentation on the under surface of the tongue, gums, or buccal mucosa.[18,22]

Keratosis

Arsenic keratosis [Figure 4] is a premalignant condition, which develops as a result of chronic arsenic exposure. It is the most sensitive early marker of arsenic toxicity. The lesions appear as multiple, firm, punctate, symmetric corn-like papules which may coalesce to form scaly, erythematous, hyperpigmented, or verrucous plaques. They are commonly located on sites prone to friction or trauma like palms and soles, but can also be present on the dorsum of extremities (dorsal keratosis), trunk, genitalia, and eyelids.[20]

Arsenic keratosis has been graded as mild, moderate, and severe types [Table 1].[22]

The most common cancer arising from arsenic keratosis is SCC. An erythematous halo and thickening around the keratosis suggests the progression of arsenic keratosis to an *in situ* SCC (Bowenoid keratosis).[20]

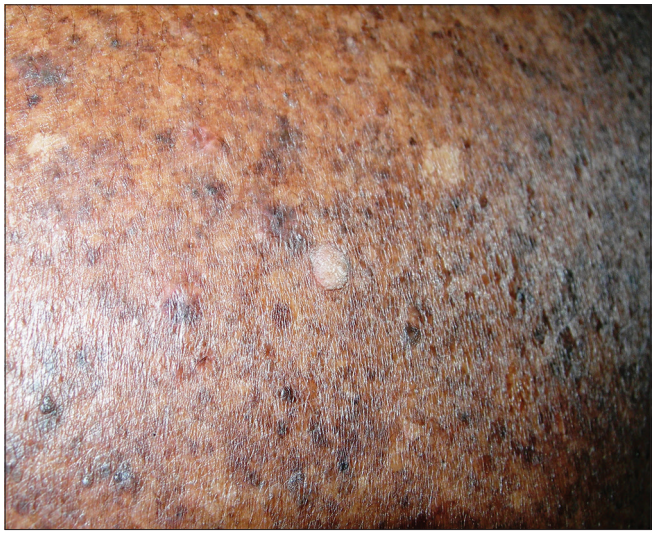

Figure 2: Rain drop pattern of hyper and hypopigmented macules as a manifestation of chronic arsenic toxicity (Image courtesy – Dr. Nilendu Sarma MD, FAAD, Associate Professor and HOD: Dr. BC Roy Post Graduate Institute of Pediatric Sciences, Kolkata, India).

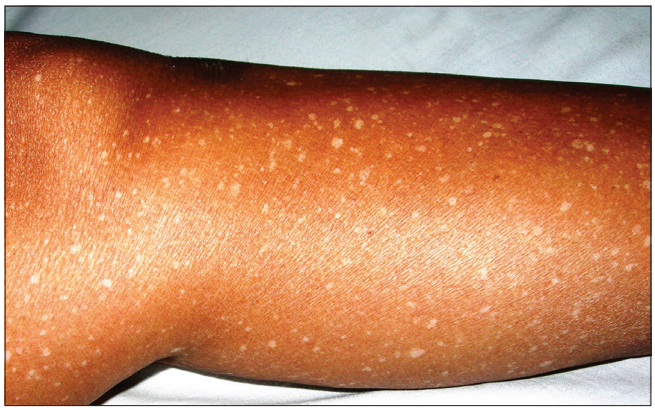

Figure 3: Hypopigmented macules as a manifestation of chronic arsenic toxicity (Image courtesy – Dr. Nilendu Sarma MD, FAAD, Associate Professor and HOD: Dr. BC Roy Post Graduate Institute of Pediatric Sciences, Kolkata, India).

Acral changes

Acrodermatitis and thromboangiitis like changes (black foot disease) can develop as late sequelae that may lead to gangrene of the legs.[20] Rarely, ulcers may develop which have a high malignant potential.[18]

Nail changes

Mees lines (white transverse bands) can be seen on all finger nails, usually after 2 months of arsenic exposure. Other nail changes reported include brownish discoloration of nails and nail dystrophy.[20]

Hair changes

Hair changes can manifest as diffuse alopecia of scalp.[6]

Cutaneous malignancies

International Agency for Research on Cancer has classified arsenic as a Class I human carcinogen.[1] Smith *et al*., suggested that the potential risk of cancer remains high even when

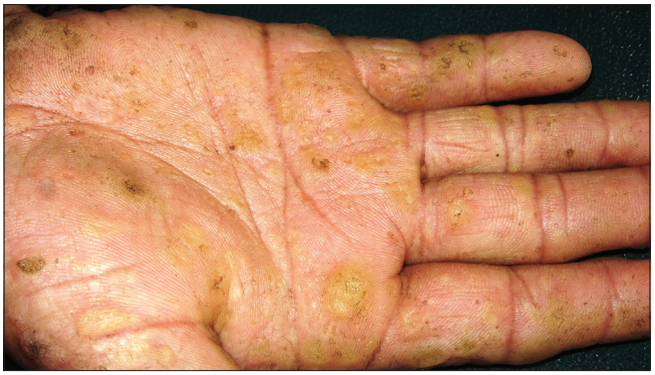

Figure 4: Multiple, firm, punctate, symmetric, corn-like papules of arsenic keratosis (Image courtesy – Dr. Nilendu Sarma MD, FAAD, Associate Professor and HOD: Dr. BC Roy Post Graduate Institute of Pediatric Sciences, Kolkata, India).

the concentration of arsenic in drinking water is within the permissible limit (reduced to 0.01 mg/L) as per the WHO recommendation in 1992.[23] Skin is considered to be the most sensitive site for arsenic-induced malignancies. They are usually multiple and can occur over both the keratotic lesions as well as on the uninvolved skin (mainly sun-protected areas). The malignancies include *in situ* and invasive SCC, basal cell carcinoma (BCC), and rarely Merkel cell carcinoma and malignant melanoma. The time interval between first arsenic exposure and cutaneous malignancy on an average is 17.8 years for Bowen's disease and superficial BCC and 19.7 years for invasive SCC.[20]

Bowen's disease

The relationship between arsenic and Bowen's disease has been studied as early as 1961 by Graham *et al*.[24] In an arsenic endemic area, Bowen's disease when detected in the sun-protected areas of the body forms the ground to search for other evidence of arsenicosis. It presents as solitary or multiple, skin colored, erythematous or pigmented, scaly macule, papule or plaque with irregular borders with a distinct demarcation line. The lesion develops a crust which when removed reveals a granular appearance with erythema and oozing.[20]

BCC

Sporadic BCC occurs predominantly on the sun-exposed areas of the body, whereas arsenic-induced Bowen's disease mostly affects the sun-protected sites. They are usually multiple in number. Superficial type of BCC (scattered over the trunk) is the most common type followed by the noduloulcerative type.[20]

SCC

Arsenic-induced SCC is locally aggressive and has a greater metastatic potential when compared to SCC originating from actinic keratosis. Arsenic-induced SCC usually occurs on the sun-protected areas and can occur *de novo* or over a pre-existing Bowen's disease/arsenic keratosis.[20]

Others

Workers who are exposed to inorganic arsenic through inhalation are prone to allergic reactions. Erythematous, exfoliative, urticarial, scarlatiniform, morbilliform, pityriasiform, lichenoid, lichen planus-like, lichen spinulosus-like, and fixed erythematous (flaring with each exposure at the same location and leaving behind hyperpigmentation) rashes are described. Arsenic also has photosensitizing properties which can cause cutaneous reactions on the sun-exposed parts of the body.[25]

Table 1: Grading of arsenic keratosis.

Severity	Size of the lesion	Characteristics
Grade 1/mild	<2 mm	Indurated and gritty papules that are palpable
Grade II/moderate	2–5 mm	Corn-like papules that are visible
Grade III/severe	>5 mm	Coalesced papules with fissures

Skin changes following acute arsenic poisoning

Transient flushing erythema, facial edema, mild pruritic, maculopapular eruption, and miliaria are seen during the initial days of exposure. Later (after 3 months), acral hyperkeratosis and lamellar desquamation appear along with nail changes such as Beau's line, Mees line, total leukonychia, dystrophy, and periungual pigmentation.[26]

Herpes simplex virus (HSV) infection was reported in a patient who survived acute arsenic poisoning.[27] HSV and herpes zoster virus reactivation are reported in patients who received arsenic trioxide for the treatment of various hematological and solid organ malignancies.[28-30] Cardenas *et al*., observed an inverse relationship between urine arsenic levels and anti-varicella zoster virus immunoglobulin G antibody levels in a representative sample of the US population.[31]

DIFFERENTIAL DIAGNOSIS

There are many conditions that can mimic the pigmentary and keratotic changes seen in arsenicosis [Table 2].[2,18,32]

HISTOPATHOLOGY

Arsenic keratosis shows epidermal changes of hyperkeratosis, parakeratosis, acanthosis, and papillomatosis. Dysplastic changes and basal pigmentation are also noted occasionally[33] Based on the absence or presence of cellular atypia, arsenical hyperkeratosis is classified into benign and malignant.[17] Arsenic-induced cutaneous malignancies do not show any specific histopathological features that could differentiate them from their non-arsenic-induced counterparts.

LABORATORY DIAGNOSIS

Testing arsenic levels in water form the mainstay of assessing the environmental burden. As per the WHO guidelines, the maximum permissible levels of arsenic in drinking water are 0.01 mg/L. In India and Bangladesh (the worst affected regions), this is kept at 0.05 mg/L.[2]

For monitoring, arsenic concentration is measured in patient's urine, hair, nails, and serum samples. The current gold standard method for arsenic analysis is atomic absorption spectroscopy which has a high specificity and

Table 2: Differential diagnosis of cutaneous arsenicosis.

Clinical manifestation	Differential diagnosis
Spotty melanosis	Freckles, lentigines, macular lichen planus, post-inflammatory pigmentation
Diffuse melanosis	Ashy melanosis, lichen planus pigmentosus, macular amyloidosis, Addison's disease, hemochromatosis
Leukomelanosis	Pityriasis versicolor, post-inflammatory hypopigmentation, epidermodysplasia verruciformis, pityriasis lichenoides chronica, idiopathic guttate hypomelanosis, leprosy, post-kala azar dermal leishmaniasis, salt-and-pepper pigmentation of systemic sclerosis
Dyschromic pattern	Dyschromatosis symmetrica hereditaria, dyschromatosis universalis hereditaria, xeroderma pigmentosum, pigmented xerodermoid, amyloidosis cutis dyschromica, generalized Dowling-Degos disease, Darier's disease
Mucosal pigmentation	Drug-induced, Peutz-Jeghers syndrome, racial pigmentation, pigmented nevus, Addison's disease
Arsenic keratosis	Verruca vulgaris, callus, pitted keratolysis, seborrheic keratosis, lichen amyloidosis, hypertrophic lichen planus, occupational keratosis, palmoplantar keratoderma

sensitivity. It measures the total organic and inorganic levels of arsenic.[3] Arsenic in urine serves as a long-term biomarker as the level does not vary significantly over time, provided that the exposure is current and ongoing. Since urine will test positive for both organic and inorganic forms of arsenic, the patient should avoid sea food items for 4 days preceding the testing. Levels of arsenic in hair and nails give an estimate of the same in the body for the preceding 9 months. The normal safe upper limit of arsenic levels in urine, hair, and nails by atomic absorption spectrophotometry was calculated as 0.05 mg/ml, 0.8 mg/kg, and 1.3 mg/kg, respectively.[3] Blood arsenic levels are not preferred as a diagnostic test since the half-life of arsenic in serum is only 2–4 hours.

Various other methods described for the detection of arsenic in water, hair, nails, and urine are colorimetric methods, inductively coupled plasma methodology, voltammetry, radiochemical methods, X-ray spectroscopy, and hyphenated techniques. However, most of these tests are semi-quantitative and of low sensitivity.[2]

Increased levels of urinary uroporphyrin III and coproporphyrin III and decreased levels of metallothionein in blood also serve as early biomarkers of arsenic toxicity.[34,35] Micronucleus induction in urothelial cells and lymphocytes indicates genetic damage induced by arsenic toxicity and is used as a biomarker for early screening of genetic damage associated with arsenic toxicity.[36]

DIAGNOSTIC CRITERIA

At present, there are no internationally accepted criteria for diagnosis and management of chronic arsenicosis.[3] However, Mazumder *et al*., had proposed a criteria that may help in the diagnosis of chronic arsenicosis based on history of exposure and clinical and laboratory findings.[37,38]

TREATMENT

Arsenic keratosis and other arsenic-induced cutaneous neoplasms can be treated using various modalities such as electrodesiccation and curettage, surgical excision, cryosurgery, oral retinoids, and topical chemotherapy. Imiquimod (5%) cream used once daily for 6 weeks has been found effective against arsenic keratosis, BCC's, and SCCs.[16]

So far, no effective therapeutic options are available for cutaneous arsenicosis. Treatment focuses mainly on supportive and preventive measures.

The treatment options tried are:

Chelating agents

Chelating agents act by binding with the metal ion, increasing its water solubility, and thus ensuring faster excretion through the kidneys. Thus, it decreases the overall arsenic load in the body and also reduces the risk of cancer. The chelating agents used for chronic arsenic keratosis and melanosis are British anti-Lewisite, penicillamine, dimercaptosuccinic acid (DMSA), and dimercaptopropane succinic acid (DMPS). They showed varied clinical outcomes with some studies showing good results and others finding them to be ineffective.[2] They are ineffective in treating arsenic-induced malignancy.

Keratolytic agents

Keratolytic agents such as urea (20%) and salicylic acid (6–10%) along with chelating agents hasten the resolution of skin lesions.[21]

Retinoids

Retinoids have been used in the treatment of arsenic keratosis due to their anti-keratinizing property. They also help in chemoprevention of arsenic-related cancers by their ability to influence the expression of genes that affect the differentiation and proliferation of cells and the induction of apoptosis.[2]

Diet and antioxidants

People who consumed high calorie diet, rich in antioxidants showed decreased effects of arsenic toxicity in spite of drinking arsenic-contaminated water. Polyphenols, green and black tea, Vitamins A, C, and E, selenium, and N-acetyl cysteine have all shown to suppress the effects of arsenic toxicity in various studies.[16] The efficacy of these agents in arsenic toxicity has not been confirmed due to lack of randomized control studies.

Photodynamic therapy

Photodynamic therapy with the application of 5-aminolevulinic acid is found effective in clearance of arsenic-induced cutaneous neoplasm.[39]

Nicotinamide

The effect of nicotinamide on arsenic and ultraviolet radiation exposed skin has been studied on *ex vivo* human skin. It was observed that nicotinamide could prevent cutaneous carcinogenesis by promoting DNA repair mechanism.[40]

PREVENTION AND CONTROL

As there is no effective treatment for chronic arsenic toxicity, prevention and control of arsenicosis play the pivotal role. The main step toward prevention is to stop consumption of arsenic-contaminated water. For this, mass awareness, periodic assessment of various aquifers, early detection of arsenicosis, and utilization of various technologies to remove arsenic contamination from drinking water are required. Rainwater harvesting, building of deep aquifers and water treatment plants to remove arsenic are some of the measures that can ensure availability of arsenic-free drinking water. Treatment of arsenic-contaminated water by methods such as coagulation, chemical oxidation, adsorption, ion exchange, membrane filtration, and reverse osmosis can remove the arsenic content.[1]

CONCLUSION

Arsenic exposure can cause varying manifestations from pigmentary skin changes to neoplasms. Its ubiquitous presence in nature makes it a challenging task to avoid exposure to this toxic metal. Being a global epidemic, global agencies such as the WHO and the United Nations Environment Program could help by promoting awareness and setting universal standards for accepted limits for arsenic exposure in day-to-day life.

Declaration of patient consent

Not required as patients' identity is not disclosed or compromised.

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Conflicts of interest

Dr. Mamatha George is on the editorial board of the Journal.

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