

Pathogenesis, clinical features and pathology of chronic arsenicosis

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ABSTRACT

Arsenicosis is a multisystem disorder, with virtually no system spared from its vicious claw; though its predominant manifestations are linked to cutaneous involvement. Cutaneous effects take the form of pigmentary changes, hyperkeratosis, and skin cancers (Bowen's disease, squamous cell carcinoma, and basal cell epithelioma). Peripheral vascular disease (blackfoot disease), hypertension, ischemic heart disease, noncirrhotic portal hypertension, hepatomegaly, peripheral neuropathy, respiratory and renal involvement, bad obstetrical outcome, hematological disturbances, and diabetes mellitus are among the other clinical features linked to arsenic toxicity. The effects are mediated principally by the trivalent form of arsenic (arsenite), which by its ability to bind with sulfhydryl groups present in various essential compounds leads to inactivation and derangement of body function. Though the toxicities are mostly linked to the trivalent state, arsenic is consumed mainly in its pentavalent form (arsenate), and reduction of arsenate to arsenite is mediated through glutathione. Body attempts to detoxify the agent via repeated oxidative methylation and reduction reaction, leading to the generation of methylated metabolites, which are excreted in the urine. Understandably the detoxification/bio-inactivation process is not a complete defense against the vicious metalloid, and it can cause chromosomal aberration, impairment of DNA repair process, alteration in the activity of tumor suppressor gene, etc., leading to genotoxicity and carcinogenicity. Arsenic causes apoptosis via free radical generation, and the cutaneous toxicity is linked to its effect on various cytokines (e.g., IL-8, TGF- β , TNF- α , GM-CSF), growth factors, and transcription factors. Increased expression of cytokeratins, keratin-16 (marker for hyperproliferation) and keratin-8 and -18 (marker for less differentiated epithelial cells), can be related to the histopathological findings of hyperkeratosis and dysplastic cells in the arsenicosis skin lesion.

Key Words: Arsenicosis, arsenic ingestion, arsenic contamination, chronic arsenic poisoning

Arsenic is known to mankind since the dawn of human civilization as an ideal homicidal poison and was used umpteen times with criminal intent.^[1] The poison was molded into a medicine in the 1700s, when Thomas Fowler developed a solution of arsenic trioxide in potassium bicarbonate (1% w/v) for the treatment of asthma, chorea, eczema, pemphigus, and psoriasis.^[2] It was also used empirically for the treatment of a variety of diseases, including leprosy, syphilis, and yaws.^[3] The art of arsenic therapy suffered a blow when this metalloid was identified as the culprit for major public health problem after exposure via drinking water in the early 1900s in Argentina, Chile, Mexico, and Taiwan.^[4] In India the problem of arsenicosis due to ground water contamination was first identified in

the state of West Bengal in 1984,^[5,6] and a survey report in 2001 suggests that around 150 million people are at risk from arsenic-contaminated ground water in the combined areas of West Bengal and its neighboring country, Bangladesh.^[7] Interestingly enough, the roller coaster of its effects and side effects is in operation even today. In spite of the pandemic of arsenic poisoning due to contaminated ground water, in a very recent development, arsenic trioxide (trisenox) has been used in the treatment of patients with acute promyelocytic leukemia^[8] and has even obtained the FDA approval in September 2000^[2] for use in the condition. The present article will highlight the problem of chronic arsenicosis with reference to its pathogenesis and clinico-pathological features.

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PATHOGENESIS OF ARSENIC TOXICITY

Arsenic is consumed mainly in 2 forms, arsenite (As^{+3}) and arsenate (As^{+5}). The absorption takes place mainly through ingestion of water, food, beverage, medicine, and sometimes, swallowing of the inhaled particulate matter with arsenic that is cleared by mucociliary escalator.^[9] Following absorption, arsenic undergoes metabolism through repeated reduction and oxidative methylation [Figure 1]. It is widely accepted that methylated metabolites of inorganic arsenic are less reactive and less genotoxic; metabolism is regarded as a bio-inactivation mechanism. Following metabolism, arsenic is rapidly cleared from blood, and only 0.1% of the arsenic remains in the plasma 24 hours after dosing. Urine is the most common route of elimination. As much as 45% to 75% of the dose is excreted in the urine within a few days to a week.^[10] The trivalent state of arsenic, As^{3+} , is widely distributed by virtue of its binding with sulfhydryl groups in keratin filament and has a tendency to accumulate in the skin, hair, nails, and mucosae of the oral cavity, esophagus, stomach, and the small intestine.^[11] On the other hand, arsenate (As^{5+}) is the predominant form deposited in the skeleton because of its ability to replace phosphate in the apatite crystal in bones; as a result of this it is retained there for a longer time.^[11] The mechanism of toxicity depends on the arsenic species and their valence state.

TRIVALENT INORGANIC ARSENIC

Mechanism of As^{+3} toxicity is essentially due to its ability to bind with the sulfhydryl groups present in various essential compounds, e.g., glutathione (GSH), cysteine, etc.^[12] The binding with function groups (e.g., thiol group) on any receptor or enzyme leads to their inactivation.^[13] This is how As^{+3} can inactivate pyruvate dehydrogenase^[14] and prevent the binding of steroids to the glucocorticoid receptors.^[15]

PENTAVALENT INORGANIC ARSENIC

As^{+5} mediates much of its toxicity after being converted to its trivalent state [Figure 1]. As^{+5} is also liable to cause direct toxicity by a mechanism called 'arsenolysis,' in which it replaces phosphate during glycolysis, resulting in ineffective generation of adenosine triphosphate (ATP).^[16]

ARSENIC AND TERATOGENICITY

Inorganic arsenic has been found to have teratogenic effects in animal studies, the principal effect being neural

tube defects, namely, exencephaly (nonclosure) and encephalocele (partial closure).^[17] Other less commonly observed teratogenicity includes failure of closure of anterior neuropore, and non-establishment of visceral yolk-sac.^[18] *In vitro* studies have shown that arsenic inhibits the development of limb buds^[19] and can also cause pharyngeal arch defect and anophthalmia.^[20]

ARSENIC AND GENOTOXICITY

Arsenic has been shown to induce sister chromatid exchanges, chromosomal aberrations, and also DNA-protein crosslinks in lymphocytes and in fibroblasts.^[21] To explain this genotoxicity, several mechanisms have been put forward, one of which emphasizes the role of reactive oxygen species in inducing the chromatid exchange.^[22] The other theory highlights the role of arsenic in impairing the DNA repair process. DNA excision repair of thymine dimer in human fibroblast is inhibited by inorganic arsenic.^[23] As^{+3} is found to inhibit DNA ligase^[24] and tubulin polymerization.^[25] It has also been shown that arsenic alters the activity of tumor suppressor gene p53 by DNA methylation.^[26]

ARSENIC AND CARCINOGENICITY

The genotoxicity induced by arsenic, as detailed above, is virtually responsible for its carcinogenicity. Hypermethylation of DNA, particularly the promoter region, results in inactivation of the tumor suppressor genes involved in DNA repair, leading to uncontrolled cell proliferation.^[27] It has been suggested that the gene product or component within the ubiquitin system is targeted by arsenic, which results in alteration leading to genotoxicity and carcinogenicity.^[28]

ARSENIC AND APOPTOSIS

Apoptosis, or programmed cell death, is a genetically determined suicidal mechanism, in which the cell participates in its own demise via a cascade of molecular interaction. Arsenic is one of the inducible toxic stimuli that trigger apoptosis via free radical generation. The cascade involves generation of reactive oxygen species, production of hydroxyl radicals, protein synthesis, and activation of protein kinase.^[29] Here comes into play the role of antioxidants in the prevention and/or treatment of arsenic toxicity. Apart from this, it has been proposed that As^{+3} induces apoptosis in leukemia cells by binding with tubulin and preventing their polymerization.^[30] This is why the scope of arsenic in the treatment of leukemia is being explored.^[8]

ARSENIC AND CUTANEOUS TOXICITY

The differentiation and proliferation of keratinocytes are under the influence of various growth factors and transcription factors that are altered by arsenic. Arsenic has been shown to stimulate interleukin (IL)-8 gene expression, and thus the secretion of IL-8, a cytokine having autocrine effect, is increased.^[31] Secretion of other growth factors, including granulocyte monocyte colony stimulating factor (GM-CSF), transforming growth factor (TGF)- β , tumor necrosis factor (TNF)- α ,^[32] and IL-1,^[33] is also increased under the influence of arsenic. Regarding the transcription factors, both AP1 and AP2 are reduced, probably through the inhibition of tyrosine phosphate.^[34] Reduced AP1 and AP2 in turn suppress the involucrin gene transcription factor, leading to reduced expression of the keratinocyte differentiation marker, involucrin.^[34] Other keratinocyte markers suppressed by arsenic include loricrin, filaggrin, sprl, and keratin-10.^[35] Among the cytokeratins, expression of keratin-16 (expressing a state of hyperproliferation) and keratin-8 and -18 (expressed in less differentiated epithelial cells) is found to be enhanced after arsenic exposure.^[36] In the organotypic culture, it has also been documented that cells show a dedifferentiated epidermal phenotype after chronic exposure to arsenic.^[36]

CLINICAL FEATURES IN ARSENIC TOXICITY

Arsenicosis is a chronic multisystem disorder arising out of high level of arsenic in the body and has been defined by the

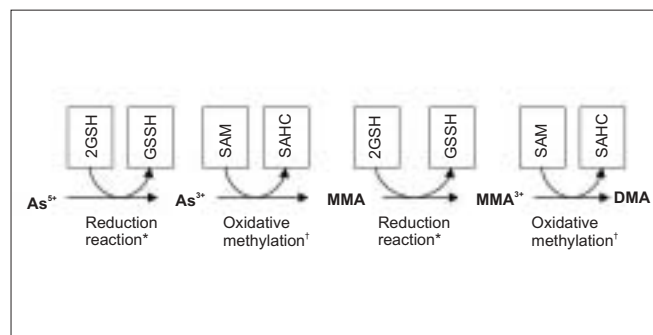


Figure 1: Metabolic transformation of arsenic in mammalian tissue (occurring mainly in liver cytosol system)

*Glutathione (GSH) acts as donor of reducing equivalent and transforms to GSSH, †Oxidative methylation involves methyl transferases (e.g., arsenite methyl transferase) with S-adenosyl methionine acting as donor of methyl (CH₃-) group. As³⁺: arsenite; As⁵⁺: arsenate; MMA: monomethyl arsonic acid [CH₃As⁵⁺]; MMA³⁺: monomethyl arsonous acid [CH₃As³⁺]; DMA: dimethyl arsonic acid [(CH₃)₂As⁵⁺]; GSH: glutathione; GSSH: glutathione after supplying reducing equivalent; SAM: S-adenosyl methionine; SAHC: S-adenosyl homo-cysteine

WHO working group 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.”^[37] The safe dose is quantified by the “maximum permissible limit” of arsenic in consumed water, which differs in different countries.^[38] The WHO guideline value for arsenic in drinking water was provisionally reduced in 1993 from 0.05 mg/L to 0.01 mg/L.^[39] Though many national authorities are seeking to reduce their limits in line with the WHO guideline value, many countries and indeed all affected developing countries still operate at present using the 0.05 mg/L standard, in part because of lack of adequate testing facilities for lower concentrations.^[39]

CUTANEOUS EFFECTS

Skin lesions are found to be the commonest and earliest manifestation in arsenicosis patients.^[40,41] In one large-scale study, 3695 (20.6%) of 18,000 persons in Bangladesh and 8500 (9.8%) of 86,000 persons in West Bengal living in arsenic-affected districts were found to show dermatological features of arsenicosis.^[42] Pigmentary changes (melanosis) and hyperkeratosis are the predominant cutaneous effects; though at times, Bowen’s disease or skin cancers may arise too.

Melanosis is found to be the earliest and the commonest of all dermatological manifestations;^[43,44] and in a study conducted in the arsenic-prevalent districts of Bangladesh, all the patients suffering from arsenicosis showed pigmentary changes.^[44] Prolonged ingestion of arsenic results in pigmentation, most intense on the trunk, which can be diffuse hyperpigmentation/melanosis;^[6,45,46] or localized (or patchy pigmentation), particularly affecting skin folds.^[45,46] Fine freckles of spotted pigmentary changes are also seen, known as ‘rain-drop pigmentation’ [Figure 2A].^[45,46] Sometimes macular areas of depigmentation may appear on normal skin or hyperpigmented background producing the distinctive appearance of ‘leucomelanosis’ [Figure 2B].^[6,45,47] Blotchy pigmentation may also involve mucous membranes such as the undersurface of the tongue or buccal mucosa.^[6,45-47]

Arsenical hyperkeratosis appears predominantly on the palms and soles, and it has been found that keratosis on the soles is the most sensitive marker for the detection of arsenicosis at an early stage.^[48] Keratoses are graded as mild, moderate, or severe depending on the extent and severity.^[45] In the early stages of keratosis (i.e., the *mild* variety), the involved skin has an indurated, gritlike

character with papules less than 2 mm in size that can be best appreciated by palpation. In the *moderate* variety, the lesions usually advance to form raised, punctate, wartlike keratoses >2-5 mm in size that are readily visible. When the keratosis becomes *severe*, it may form keratotic elevations more than 5 mm in size and sometimes become confluent and diffuse [Figure 3A] and sometimes result in cracks and fissures too.^[43,49] Though palms and soles are primarily affected by hyperkeratosis, dorsa of the extremities [Figure 3B] and trunk may also be affected by it. It has also been observed that palmar keratosis occurs early before people develop arsenic-related cancers of bladder and lung; thus it can act as an early marker of carcinogenicity.^[50]

Skin cancer in chronic arsenicosis is quite distinctive and can arise in the hyperkeratotic areas, as well as appear on non-keratotic areas of the trunk, extremities, or head.^[51,52] Skin is thought to be perhaps the most sensitive site for arsenic-induced malignancies.^[53] The lesions are frequently multiple and involve covered areas of the body; unlike non-arsenical skin cancer, which usually presents as a single lesion and which occurs frequently on the exposed parts of the body.^[54,55] Arsenic exposure has been associated with 3 types of skin cancers, namely, Bowen's disease [Figure 4A], basal cell carcinoma [Figure 4B], and squamous cell carcinoma [Figure 4A].^[56] It has been suggested that human papilloma virus (HPV) infection could constitute an additional risk factor for the development of non-melanoma skin cancer in humans chronically exposed to As.^[57] There are also published reports of Merkel cell carcinoma,^[58]

sometimes arising in association with Bowen's disease^[59,60] in patients with chronic arsenicosis. It has been suggested that in individuals with documented arsenic-induced Bowen's disease, more aggressive screening for long-term complications, especially the development of subsequent visceral malignancies (viz., small cell carcinoma of lungs, etc.), should be done.^[61] There is also a study which has demonstrated an increased risk of melanoma in persons with elevated toenail arsenic concentrations,^[62] raising the issue relating to the role of arsenic in the development of melanoma.

EXTRACUTANEOUS EFFECTS

Apart from cutaneous manifestations, arsenicosis causes myriads of other symptoms, including generalized weakness; anorexia and weight loss; anemia; and symptoms relating to the involvement of the lungs, gastrointestinal system, liver, spleen, genitourinary system, hemopoietic system, eyes, nervous system, and cardiovascular system [Figure 5].^[63] The proposed mechanisms of pathogenesis for these extracutaneous manifestations are highlighted in [Table 1].^[64-75]

Vascular effects

Arsenic has been identified as a major contributing risk factor for development of ischemic heart disease; as well as blackfoot disease, a unique peripheral vascular disease that was endemic to the southwestern coast of Taiwan.^[76] Blackfoot disease, a unique peripheral arterial disease

Table 1: Proposed mechanism of pathogenesis for extracutaneous involvement in arsenicosis

Systemic involvements	Proposed mechanism of pathogenesis
Atherosclerosis	<ul style="list-style-type: none"> • Monoclonal expansion of smooth muscle cell.^[64] • Production of reactive oxygen species (H₂O₂ and -OH radical) → endothelial cell proliferation^[65] and apoptosis.^[66] • Upregulation of inflammatory signal → release of TNFα from mononuclear cells or stimulates cyclooxygenase II pathway.^[67] • Enhances arterial thrombosis and platelets aggregation^[68]
Hepato-toxicity (fibrosis)	<ul style="list-style-type: none"> • Predominant lesion of hepatic fibrosis appears to be induced by oxystress and elevation of cytokines (TNF-alpha and IL-6) associated with increasing level of collagen in the liver.^[69] • Reduction/weakening of hepatic glutathione and enzymes of antioxidant defense system of liver → free radicle accumulation → peroxitativ damage of lipid membrane.^[70]
Respiratory system	<ul style="list-style-type: none"> • Pathophysiology is not well understood but oxidative damage is thought to play a role. • Arsenic is potent respiratory toxicant and ingested arsenic can reach respiratory tract to damage lung tissue.^[71]
Neurological	<ul style="list-style-type: none"> • Predominantly sensory with distal axonopathy due to axonal degeneration.^[72]
Genitourinary	<ul style="list-style-type: none"> • Renal tubular necrosis, nephritis and nephrosis^[73]
Diabetes mellitus	<ul style="list-style-type: none"> • As³⁺ suppress insulin stimulated glucose uptake by interfering the mobilization of glucose transporters in adipose cell.^[74] • Interfering the transcription factor involved in insulin related gene expression.^[75]



Figure 2A: Rain-drop pigmentation with areas of Bowenoid changes over the right shoulder and right side of chest



Figure 2B: Leucomelanosis



Figure 3A: Severe variety of arsenical hyperkeratosis



Figure 3B: Arsenical hyperkeratosis involving the dorsa of hands



Figure 4A: Squamous cell carcinoma affecting the hands, with Bowen's disease on the abdomen



Figure 4B: Basal cell carcinoma behind the ear, with arsenical keratosis on the palms

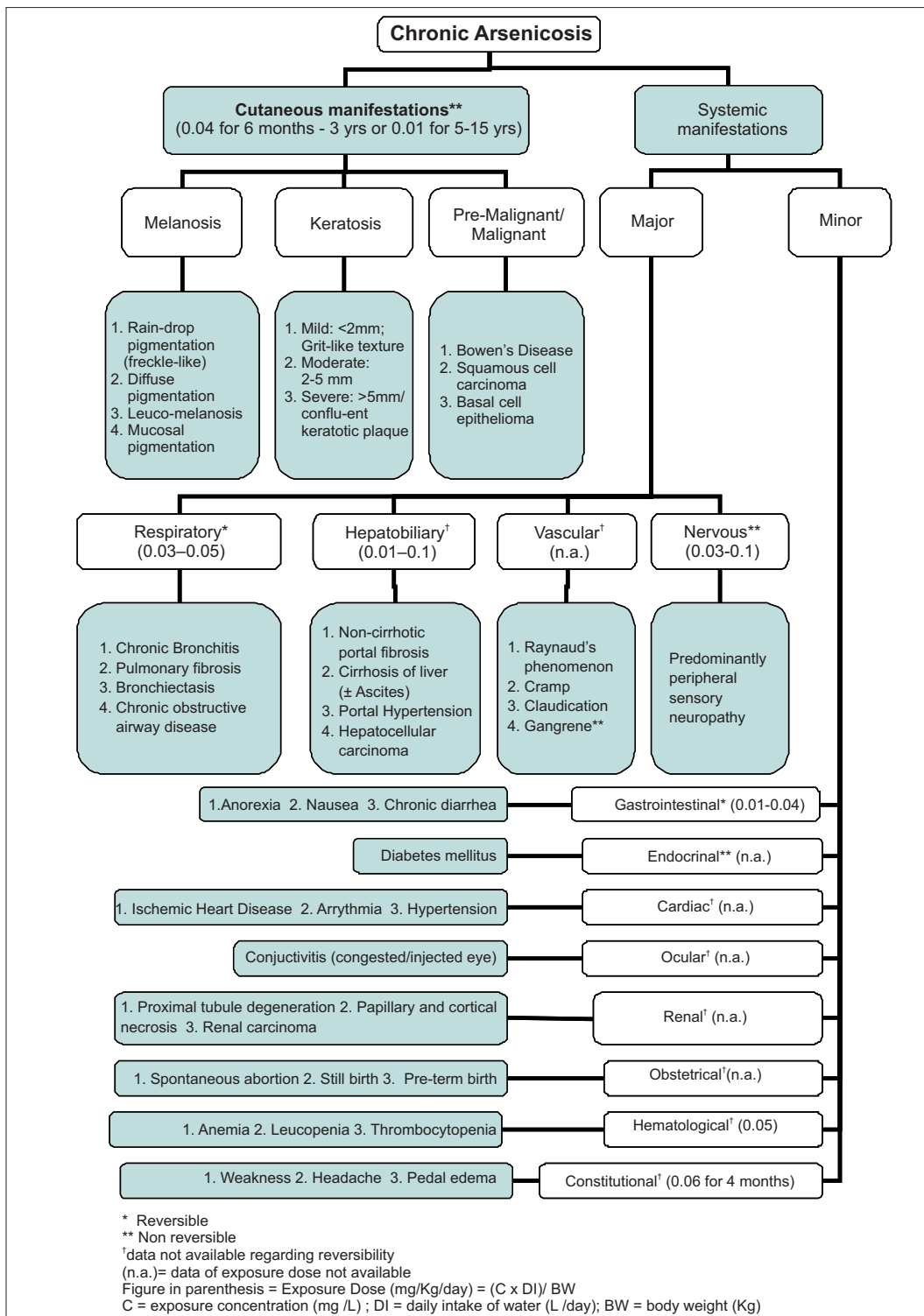


Figure 5: Clinical manifestations of chronic arsenicosis^[63]

characterized by severe systemic arteriosclerosis resulting in dry gangrene and spontaneous amputations of affected extremities at end stages, is characteristically found in areas where residents imbibed artesian well water containing high amounts of arsenic for a long period.^[54,76] Diagnostic criteria for blackfoot disease include objective signs of ischemia,

viz., absence or diminution of arterial pulsation, pallor on elevation or rubor on dependency of ischemic extremities, and various degrees of ischemic changes in the skin; as well as subjective symptoms of ischemia, viz., intermittent claudication, pain at rest, and ischemic neuropathy.^[54,77] In spite of the fact that not all persons living in arsenic-

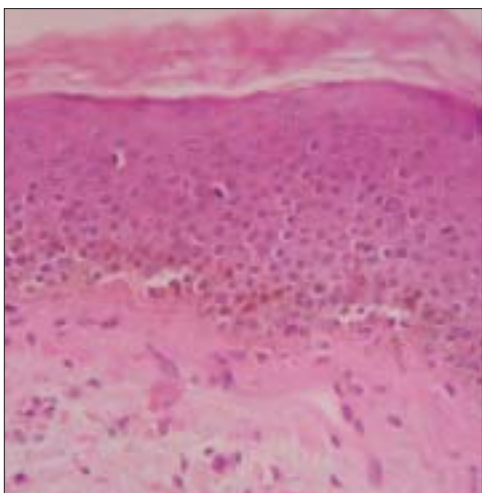


Figure 6A: Histopathology of arsenical keratoses showing hyperkeratosis, acanthosis, increased pigments in the basal layer with no cellular atypia, type A (H and E, x100)

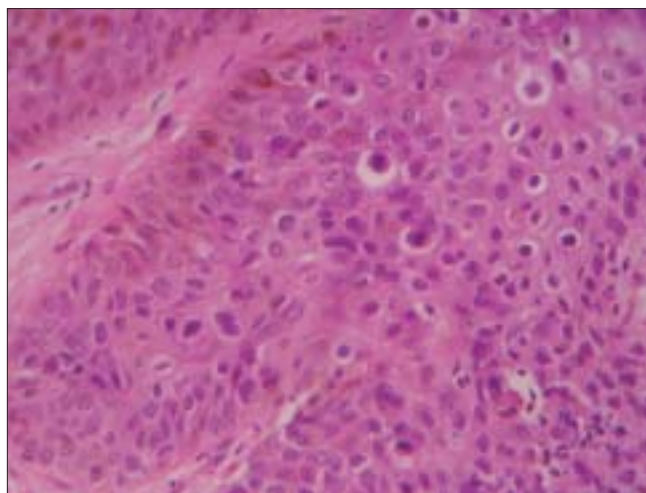


Figure 6B: Dysplastic keratinocytes (presence of anisocytosis and mitotic figures) with dyskeratosis, type B (H and E, x400)

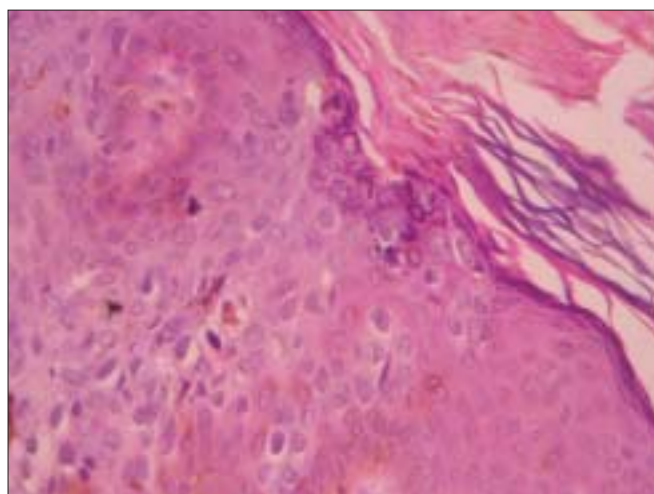


Figure 6C: Parakeratotic hyperkeratosis with focal hypergranulosis, increased basal layer pigmentation, and early dysplastic change, type B (H and E, x400)

prevalent areas are affected with black, mummified dry gangrene,^[78] subclinical arterial insufficiency and defects in cutaneous microcirculation can be demonstrated in seemingly normal subjects living in the endemic villages.^[77] Extensive pathological study showed that 30% of blackfoot disease patients had histological lesions compatible with thromboangiitis obliterans, and 70% showed changes of arteriosclerosis obliterans.^[79] Marked generalized atherosclerosis was observed in all autopsied cases of blackfoot disease.^[79] A dose-response relationship between cumulative arsenic exposure and subclinical peripheral vascular disorder has been shown among seemingly normal subjects even after cessation of drinking artesian well water in the endemic area of blackfoot disease in Taiwan.^[80]

The vascular effects of chronic arsenic poisoning are not

only limited to peripheral vasculature but may also involve cardiovascular and cerebrovascular systems as well, leading to hypertension,^[81] ischemic heart disease,^[82] cerebrovascular disease,^[83] and carotid atherosclerosis.^[84]

GASTROINTESTINAL (GI) EFFECTS

The chronic absorption of arsenic occasionally produces hepatocellular toxicity, which may be the result of an inhibition by arsenic of the enzymes involved in cellular metabolism.^[56] Gastric symptoms, including nausea, loss of appetite, constipation, or sometimes diarrhea, are also reported as a result of chronic arsenicosis.^[56] Noncirrhotic portal fibrosis is found to be the predominant lesion in liver histopathology.^[70,85,86] The portal fibrosis is characterized by expansion of portal zones with streaky fibrosis, a few of which contained leash of vessels.^[70] Hepatomegaly was also found to be significantly higher in arsenic-exposed people, and the incidence of hepatomegaly was found to have a linear relationship proportionate to increasing exposure of arsenic in drinking water in both sexes.^[70,85,86] However, portal hypertension was found in a smaller number of cases.^[70]

In the large-scale study with 7683 people from arsenic-affected districts of West Bengal, 10.2% ($P < 0.001$) of 4216 subjects with high arsenic exposure showed hepatomegaly; and in the hospital setting, among 248 cases, hepatomegaly was seen in 76.6% and noncirrhotic portal fibrosis in 91.3% of the subjects.^[70] In another study, continued arsenic feeding resulted in fatty liver with elevated serum aminotransferases at 12 months and hepatic fibrosis at 15 months.^[85]

NERVOUS SYSTEM EFFECTS

Peripheral neuropathy is the predominant neurological complication in patients of arsenicosis; and overall, sensory features were more common than motor features in patients of neuropathy.^[72] Arsenic neuropathy has been classified as a distal axonopathy with axonal degeneration, especially of large myelinated fibers of both sensory and motor neurons.^[87] Signs and symptoms accompanying arsenical neuritis are essentially paresthesias (*viz.*, burning, tingling sensations), pain, and tenderness in the affected limb with or without distal limb weakness and atrophy; and absent or diminished tendon reflexes.^[56,72] In one of the studies, nerve conduction and electromyographic studies revealed dysfunction of sensory nerves in most cases; whereas visual evoked potential and brainstem auditory evoked potential findings were mostly normal.^[86] Another study revealed characteristic electromyographic changes, including decreased nerve conduction amplitude but little changes in nerve conduction velocity.^[88]

RESPIRATORY SYSTEM EFFECTS

The respiratory symptoms resulting from arsenicosis have been shown to demonstrate dose-related symptoms, including cough, shortness of breath with the breath sounds revealing crepitations and/or rhonchi.^[89] These respiratory effects were most pronounced in individuals exposed to high concentrations of arsenic in water and who also had concomitant skin lesions.^[89]

OTHER SYSTEMS

Urine may be red or green in color; and in some cases, dysuria and anuria develop from renal tubular necrosis.^[56] Studies have documented an adverse obstetrical outcome in patients of arsenicosis, with increased incidence of spontaneous abortions, stillbirths, preterm births; and high perinatal and neonatal mortality.^[90-92] Transplacental transfer of arsenic is a major concern, since there are reports of fetal death resulting from arsenic poisoning in pregnant women.^[93,94] Studies found that arsenic concentrations were similar in cord blood and maternal blood, suggesting that arsenic can readily cross the placenta.^[95,96]

Chronic exposure to arsenic has been associated with disrupted erythropoiesis with subsequent development of anemia, leucopenia, and thrombocytopenia.^[56] There is evidence indicating that ingestion of arsenic may predispose a person to the development of diabetes mellitus.^[97,98] The

incidence of diabetes mellitus in arsenic-hyperendemic villages of Taiwan correlated with age, body mass index, and cumulative arsenic exposure.^[98] A study conducted in Bangladesh also found statistically significant association between diabetes mellitus and exposure to arsenic.^[99]

CARCINOGENICITY

Skin, lung, bladder, kidney, prostate, liver, uterus, and possibly lymphatic tissues are considered as sites for arsenic-induced malignancies, and the skin is thought to be, perhaps, the most sensitive site.^[56,100]

ARSENICOSIS AND NUTRITIONAL STATUS

The role of nutritional factors in arsenic metabolism and toxicity is not clear. Recent studies have focused on the role of nutrients and composition of diet in the GI absorption of arsenic. It has been shown that arsenic and various minerals and nutrients utilize the same transport mechanism at the intestinal level.^[101] It is noted that increasing concentration of As^{3+} and As^{5+} causes dose-dependent decrease in the intestinal absorption of water, sodium, glucose, and leucine.^[102] The inhibition in absorption is competitive in nature, As^{3+} being fivefold potent than As^{5+} .^[102] Conversely, improving the nutrient intake would reduce the GI absorption and its subsequent toxicities. It has been documented that addition of phosphates in diet can decrease the intestinal uptake^[101] and even renal tubular re-absorption of As^{5+} .^[103]

Limited studies have indicated that poor nutritional status may increase the risk of arsenic-related health effects.^[104] In a study in West Bengal, India, it was found that participants with poor nutritional status (weight below 80% of the standard body weight for their age and sex) had an overall 1.6-fold increase in the prevalence of keratoses, suggesting that malnutrition may increase the susceptibility for arsenic toxicity.^[105] Arsenic-affected people of southwestern Taiwan^[106] and northern Chile^[107] were also reported to have a low socioeconomic status and poor nutritional status. It has also been suggested that low dietary selenium ingestion and accelerated selenium depletion by arsenic are the possible contributing factors to chronic arsenicosis.^[108]

Not only does the malnutrition favor development of arsenicosis, the disease itself leads to derangement of energy utilization. As^{+5} can substitute inorganic phosphate in the synthesis of ATP and thus can uncouple oxidative phosphorylation in mitochondria.^[109] Glycolysis can also be

inhibited by As^{+5} by the virtue of its ability to compete with phosphate to form the dysfunctional compound 1-arseno-3-phosphoglycerate instead of 1,3-diphosphoglycerate.^[110]

HISTOPATHOLOGY OF CHRONIC ARSENICOSIS SKIN LESIONS

There is real dearth of reports regarding the types and patterns of histopathological changes in skin lesions of chronic arsenicosis. The histopathological study from Bangladesh^[111] wherein hyperkeratotic lesions of 70 patients with chronic arsenicosis were compared with 20 controls, revealed hyperkeratosis (100%), parakeratosis (97%), acanthosis (95.7%), and papillomatosis (74%) to be significantly more ($P < 0.001$) in the patients than in controls. They also found basal cell pigmentation in 42.8% ($P > 0.05$) and dysplasia and malignant changes in 7% ($P > 0.1$). Another study, also from Bangladesh,^[112] documented hyperkeratosis, parakeratosis, acanthosis, papillomatosis, hypergranulosis, and dysplastic changes to be the most important and constant findings; and on the other hand, basal pigmentation and dermal changes, to be the inconstant features. Study on the neoplastic manifestations of arsenicosis revealed pre-cancerous skin lesions in 6.6% and cancerous lesions in 0.8% of the patients.^[113] Arsenical hyperkeratosis has been classified histologically into benign type A [Figure 6A] and malignant type B according to the absence or presence of cellular atypia [Figures 6B, 6C].^[114] None of the available studies focused on the histopathology of the pigmented lesions.

A study of histopathology of 20 cases of arsenicosis from West Bengal revealed hyperkeratosis in 16 (80%), acanthosis in 6 (30%), parakeratosis in 2 (10%), elongation of rete ridges in 2 (10%), basal cell epithelioma in 2 (10%), squamous cell carcinoma in 1 (5%), and normal pattern in 4 (20%) patients.^[115] Masson Fontana's stain from the melanotic lesions of those 20 patients revealed pigmentation of basal layer in 6 (30%), pigment dropout in dermis in 4 (20%), and normal pattern of pigment in 14 (70%) patients.

CONCLUSION

Arsenicosis is primarily diagnosed on the basis of its cutaneous manifestations, but the manifestations can, at times, be confused with other dermatoses. Hence a high index of suspicion, especially in those people who hail from a region with arsenic contamination in ground water, is required. The systemic manifestations also help in corroborating the cutaneous findings and can be useful when the dilemma exists in the diagnosis.

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