

Pathology Related to Chronic Arsenic Exposure

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Millions now suffer the effects of chronic arseniasis related to environmental arsenic exposure. The biological mechanisms responsible for arsenic-induced toxicity and especially chronic effects, including cancer, are not well known. The U.S. Armed Forces Institute of Pathology (AFIP) is participating in an international research effort to improve this understanding by the development of the International Tissue and Tumor Repository for Chronic Arsenosis (ITTRCA). The ITTRCA obtains, archives, and makes available for research purposes, tissues from subjects exposed to arsenic. We provide here a short overview of arsenic-induced pathology, briefly describe arsenic-induced lesions in the skin and liver, and present five case reports from the ITTRCA. Arsenic-induced skin pathology includes hyperkeratosis, pigmentation changes, Bowen disease, squamous cell carcinoma, and basal cell carcinomas. A unique spectrum of skin lesions, known as arsenical keratosis, is rather characteristic of chronic arseniasis. Bowen disease, or squamous cell carcinoma *in situ* of the skin, has been well documented as a consequence of arsenical exposure. A spectrum of liver lesions has also been attributed to chronic arseniasis. Of these, hepatocellular carcinoma, angiosarcoma, cirrhosis, and hepatoportal sclerosis have been associated with arsenic exposure. We present case reports that relate to these health conditions, namely, squamous cell carcinoma, basal cell carcinoma, and Bowen disease of the skin and hepatocellular carcinoma and angiosarcoma of the liver. Four patients had been treated with arsenical medications for such conditions as asthma, psoriasis, and syphilis, and one case occurred in a boy chronically exposed to arsenic in drinking water. **Key words:** angiosarcoma, arsenic, Bowen disease, hepatocellular carcinoma, hepatoportal sclerosis, hyperkeratosis, liver, noncirrhotic portal fibrosis, squamous cell carcinoma. *Environ Health Perspect* 110(suppl 5):883–886 (2002).

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It has been recognized for centuries that arsenic exposure can cause acute toxicity, including death. Its propensity to cause chronic toxicity and cancer via environmental exposure at low doses has now become apparent. Arsenic has a long history of use as an intentional poison, in medicines and pesticides, and it is still found in folk medicines and pesticides in many countries. Until other therapies became available (in the late 1940s), syphilis and psoriasis were often treated with arsenicals.

Interest in environmental arsenic has dramatically increased in recent years. This stems from the pollution of drinking water and other environmental media in geographic areas. Millions now suffer from the effects of chronic arseniasis, which represents a major international public health dilemma. The potential for cancer is a very major concern. The U.S. National Research Council has recently concluded, based on epidemiologic studies, that the evidence is now sufficient to include lung and bladder cancer, along with the skin cancers, as being caused by ingestion of inorganic arsenic (1). They further concluded that there is some indication that arsenic may induce cancers in other organs, although the evidence is not as strong.

Chronic arsenic exposure has been implicated in several noncancerous conditions, in

particular, skin disease, diabetes mellitus, hypertension and cardiovascular disease, perturbed porphyrin metabolism, and irreversible noncirrhotic portal hypertension (1). It has been long known that arsenic exposure is associated with skin pathology, including hyperpigmentation, hyperkeratosis, and skin cancers. In the majority of cases in which an internal cancer has been ascribed to arsenic exposure, a dermatologic hallmark of arsenic poisoning was also identified (2).

Effects of arsenic on the liver have been suggested in a few case reports, although the pathology has not been well described. In addition to noncirrhotic portal hypertension (3), other liver pathology has been described, including hepatic enlargement, hepatocellular carcinoma (4), and liver angiosarcoma (5). Epidemiologic studies have not confirmed the association between arsenic exposure and hepatocellular carcinoma and liver angiosarcomas. In this article we present two cases of liver cancer that appear to be associated with arsenic exposure, one involving a hepatocellular carcinoma and the other a liver angiosarcoma.

Materials and Methods

One impediment to better treatment and prevention of chronic arsenic-induced toxicity and cancer is the rudimentary knowledge of

the responsible biological mechanisms. Further, the exact nature of the carcinogenic action of arsenic is not clear (1). As part of an international effort to gather information and conduct research along this line, the U.S. Armed Forces Institute of Pathology (AFIP), with the support of the U.S. Environmental Protection Agency, the National Cancer Institute, and the National Institute of Environmental Health Sciences has developed the International Tissue and Tumor Repository for Chronic Arsenosis (ITTRCA) (6).

The diagnostic criteria for arsenic-induced pathology has not been standardized because of the large spectrum of lesions that may be present in arsenic-exposed persons and also because of the lack of an international agreement on the criteria for diagnosis of the lesions. The ITTRCA is striving to obtain, archive, and make available for research purposes, tissues from subjects exposed to arsenic. Histopathologic material submitted to the ITTRCA includes surgical and autopsy specimens from patients exposed to drugs or environmental substances. In addition to tissues, clinical information for each patient was furnished by the contributing facilities. The specimens were stained with routine histochemical stains, usually hematoxylin and eosin, with additional diagnostic studies such as immunohistochemistry performed as needed.

ITTRCA hopes to contribute to an understanding of chronic arseniasis, and toward this end we are evaluating the

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pathology in a series of arsenic-exposed cases. In addition to the two cases of liver cancer, we briefly describe the most common arsenic-induced lesions found in skin, based on three other case reports. All five cases are from the ITTRCA, and the pathology is considered highly probable to have been induced by chronic arsenic exposure.

Presentation and Discussion of Cases

Arsenic-Induced Skin Lesions

Arsenic tends to concentrate in ectodermal tissues, including the skin, hair, and nails, even with low-level exposures. Thus, the skin is a primary target organ for chronic arsenic toxicity. Epidemiologic studies have conclusively confirmed arsenic-induced cancers of the skin. In nearly all cases where internal cancers are attributed to arsenic exposure, there has been cutaneous evidence of arsenic exposure in the form of arsenical keratosis, hyperpigmentation, and multiple cutaneous malignancies (7). Arsenical keratosis is a well-established clinical syndrome, characterized by several specific pathological features, including hyperkeratosis, parakeratosis, arsenical pigmentation, and squamous cell carcinoma *in situ*. Arsenical keratosis is most pronounced on the feet and hands, although it can occur on the trunk and other areas of the extremities. In early stages of arsenical keratosis, the presence of squamous cell carcinoma *in situ* may not be evident. Bowen disease is squamous cell carcinoma *in situ* of the skin, precancerous in nature, and sometimes associated with arsenic exposure.

The most common arsenic-induced skin cancers are squamous cell carcinomas and basal cell carcinomas. Squamous cell carcinomas are true invasive carcinomas of the surface epidermis, consisting of irregular masses of epidermal cells that proliferate downward and invade the dermis. Basal cell carcinomas are tumors that arise from characteristic cells, often referred to as basaloma cells. They have a large, oval or elongated nucleus with relatively little and poorly defined cytoplasm.

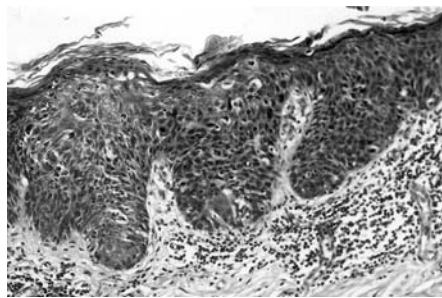


Figure 1. Bowen disease. Atypical and pleomorphic keratinocytes with scattered mitotic figures are present at all levels of the hyperplastic epidermis.

Histologically, tumors associated with arsenic exposure do not differ from tumors unrelated to arsenic. Designating arsenic as the causative agent of these skin cancers frequently relies on the location of these tumors in sun-protected areas (because exposure to the sun is the most common cause of skin cancer) and the presence of other signs of arsenic exposure (e.g., hyperkeratosis and hyperpigmentation). We are presenting three ITTRCA cases that demonstrate these arsenic-induced skin lesions.

Case 1. A 76-year-old woman had a history of taking Fowler's solution for psoriasis for an unknown period of time. Fowler's solution (1% potassium arsenite, an inorganic arsenic solution) was used as a treatment for a variety of medical disorders, including psoriasis and syphilis. She presented with an ulcerated lesion of the left breast that had been present for a number of years. A biopsy was performed and the pathology showed Bowen disease of the breast (Figure 1). The lesion was interpreted as a squamous cell carcinoma *in situ* consistent with Bowen disease. The entire thickness of the epithelium showed dyskeratosis, disorientation of the cells, and acanthosis. There was no histologic evidence of solar damage in the examined material.

Case 2. In this case, a 47-year-old female was treated with Fowler's solution as a child for persistent eczema. She developed squamous cell carcinoma of the middle finger that resulted in amputation at the metatarsal phalangeal joint. She apparently healed well, but 3 years later, keratosis developed at the suture line. The squamous cell tumor consists of disorderly foci of atypical squamous cells proliferating into the dermis (Figure 2). The dermis shows a moderate inflammatory reaction.

Case 3. A 37-year-old man was treated for asthma for 2 years with a medication suspected to contain arsenic. He developed multiple keratotic lesions of the right fingers and breast. In addition he developed basal cell carcinoma of the neck (Figure 3). Arsenic is one of the main causes of basal cell carcinomas in sun-protected areas, of which 90% occur on the head and neck. A biopsy of the

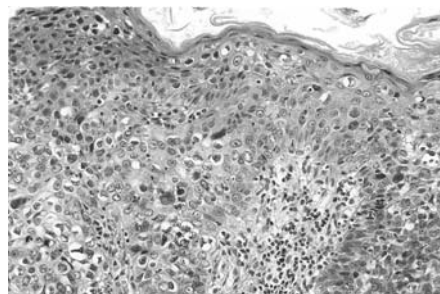


Figure 2. Squamous cell carcinoma. Pleomorphic, atypical keratinocytes extend into the dermis.

basal cell carcinoma showed elongations of the epidermis downward into the dermis with nuclear palisading of the peripheral layer.

Arsenic-Induced Liver Lesions

Two types of liver cancer have been associated with arsenic exposure: hepatocellular carcinoma and angiosarcoma of the liver. Hepatocellular carcinomas have been clearly associated with ingested inorganic arsenic since the early 1990s (8,9). Histologically, hepatocellular carcinomas range from well differentiated to quite anaplastic undifferentiated lesions. In the moderately to well-differentiated types, trabeculae are more than two or three cells thick and are composed of tumor cells that exhibit round to oval nuclei with a high nuclear/cytoplasmic ratio and prominent nucleoli. They are surrounded by sinusoidal spaces. The malignant cells often have an abundant eosinophilic cytoplasm and may contain bile, fat, glycogen, or cytoplasmic inclusions. In addition, other clues helpful in diagnosis are the presence of mitoses, tumor within vascular structures, and infiltration of tumor into adjacent liver.

Angiosarcoma of the liver (hemangioendothelial sarcoma) is a malignant neoplasm of the liver constituting only 2% of all primary liver tumors in Western countries. Researchers have become more interested in this disease because of its relationship with environmental carcinogens such as vinyl chloride monomer, thorium dioxide, and inorganic arsenic (10). The relationship of chronic arsenic intoxication to angiosarcoma of the liver has been well documented. Roth (11) described the correlation between hepatic angiosarcoma and arsenic-containing pesticide exposure in German vineyard cultivators in the 1940s and 1950s. Regelson (12) was the first to report a similar case in the American literature. A nationwide review of deaths from angiosarcoma of the liver identified seven cases with a history of prolonged use of Fowler's solution, which provided further support for the association between chronic arsenic exposure and angiosarcoma. Several reports in the literature

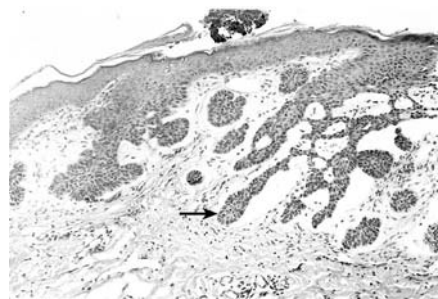


Figure 3. Basal cell carcinoma. Elongations of the epidermis downward into the dermis with nuclear palisading of the peripheral cell layer can be observed (arrow).

have followed those seminal papers, one of which documents a case of angiosarcoma and hepatoportal sclerosis (HS; also known as noncirrhotic portal hypertension) in the same patient with chronic arsenic salt exposure (13). The latent period in these studies varied from 13 to 29 years.

Case 4. A 32-year-old white male was treated with Fowler's solution for dermatitis herpetiformis. He used the medication daily for 3 years, 10 years prior to admission to a hospital for pain in the epigastric region. The clinical record indicates that he developed "arsenic poisoning." Skin lesions characteristic of arsenical keratosis were recorded at that time. In addition his liver was noted to be enlarged. There was no reported history of alcohol use. Serologic studies were negative. He died 2 months after admission, and an autopsy attributed death to hepatic insufficiency. Examination of the liver at autopsy revealed an enlarged liver (weight, 6,250 g) with a large hemorrhagic and necrotic nodule occupying two thirds of the liver. Microscopic sections of liver showed necrosis and a malignant epithelial-type tumor, diagnosed as hepatocellular carcinoma (Figure 4). The tumor cells show considerable pleomorphism and eosinophilic cytoplasm. The nuclei are irregular, hyperchromatic, and occasionally multinucleated. Associated cirrhosis can be observed.

Case 5. A 14-year-old boy lived in an area of Argentina where the water was contaminated with arsenic. Since 5 years of age, he had typical arsenic-induced lesions involving the soles and palms. Initially, the lesions consisted of hypochromatic macules that later developed into hyperkeratotic lesions. The boy was admitted to the hospital with symptoms suggestive of liver disease. Liver tests performed at that time confirmed liver disease, which progressed rapidly with a fatal outcome. Autopsy revealed an enlarged liver with a large necrotic, hemorrhagic tumor in the right lobe. Histologic examination revealed malignant endothelial cells consistent with the diagnosis of angiosarcoma of the liver (Figure 5). Microscopically, there was

diffuse proliferation of atypical endothelial cells infiltrating into existing sinusoidal spaces. The diagnosis was confirmed with immunohistochemical studies.

Hepatoportal Sclerosis

Hepatoportal sclerosis (also known as noncirrhotic portal fibrosis, idiopathic portal hypertension, and Banti syndrome) is a condition characterized by portal hypertension without evidence of liver cirrhosis. In HS there is no evidence of extrahepatic portal vein obstruction or relation to congenital hepatic fibrosis or to any blood, parasitic, or granulomatous diseases or other known diseases (14). Clinically, HS is manifested by splenomegaly, anemia, and episodes of gastrointestinal hemorrhage due to esophageal varices. HS is a rare but relatively specific condition that may occur after years of arsenic ingestion at concentrations of 0.01 mg/kg/day.

Histologically, HS is characterized by thickening and sclerosis of the wall of large portal vein branches. Increased perivascular fibrosis is seen in the portal tracts, which may show obliteration or sclerosis of portal vein branches. The portal vein lumen is reduced, and organized thrombi with recanalization may be seen. The bile ducts may show concentric periductal fibrosis. Lobular architecture is maintained with some mild fibrous bridging between the portal areas and the portal and central areas.

Although the etiology of HS is usually not known, chronic arsenic ingestion has been associated with the development of the disease in several different reports. Nevens et al. (3) described eight patients with noncirrhotic portal hypertension who had been treated for psoriasis and had received Fowler's solution some years previously. Total arsenic intake was estimated to vary from 4 to 16 g, with an interval between the treatment and onset of symptoms of 2–16 years. These patients showed the characteristic arsenical skin changes of keratosis and melanosis, with malignant skin cancers present in four of the patients. Datta et al. (15) reported nine patients from northern India

with HS that had consumed high levels of arsenic from contaminated drinking water, adulterated opium, and indigenous medicines. Typical signs of arseniasis were observed along with high levels of arsenic in the majority of the livers of these patients. These reports support the hypothesis that arsenic may cause HS by damage to the intrahepatic portal veins.

Arsenic-Induced Cancers in Other Organs

The evidence for other arsenic-induced cancers has come from epidemiologic studies because there are no suitable animal models to conduct research on these issues. According to a recent epidemiologic study of an area of Taiwan with endemic blackfoot disease, high mortality was found in males and females for lung, bladder, kidney, and nasal cancers and possibly cancers at other sites in addition to those of the skin and liver. Generally speaking, the outcomes of this study corroborate the results of several other studies suggesting a relationship between arsenic exposure and cancers of the internal organs (16). For example, arsenic has been implicated as a bladder carcinogen in separate studies from Argentina, Chile, and Taiwan (17). In addition, the results of a recent study in Cordoba, Argentina, add to the evidence that arsenic ingestion increases the risk of kidney cancers (18). An association between carcinoma of the lung and inhaled arsenic is well established; more recent studies have shown that ingested arsenic may also be an etiologic factor in the development of lung cancer (19).

Other Noncancer Effects of Chronic Arsenic Poisoning

As previously indicated, increased risks for a variety of arsenic-induced noncancer effects have been suggested. This includes peripheral vascular disease, cardiovascular disease, diabetes mellitus, neurologic effects, chronic lung diseases, diminished hearing, and cerebrovascular disease (1,2,20–24). It is quite apparent that the hazardous effects of arsenic are multiorgan related with extensive systemic pathology.

Although reproductive effects of arsenic in humans have not been extensively investigated, there is evidence from both animal and human studies that suggests reproductive toxicity from arsenic. The human data are still sparse, and the results from laboratory experiments in animals are not conclusive. The few human studies suggest that arsenic exposure may increase the incidence of pre-eclampsia in pregnant women, decrease birth weight of newborn infants, and increase the risk of malfunctions and stillbirths as well as spontaneous abortions (25). Recent laboratory studies suggest an increase in malformations and stillbirths in animals (26,27); however, the effects

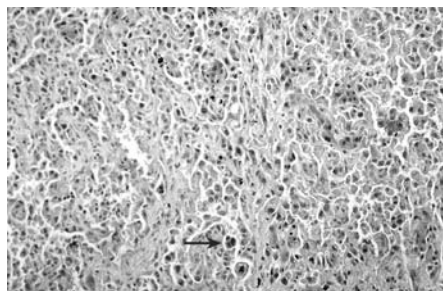


Figure 4. Hepatocellular carcinoma. The nuclei are irregular, hyperchromatic, and occasionally multinucleated (e.g., arrow).

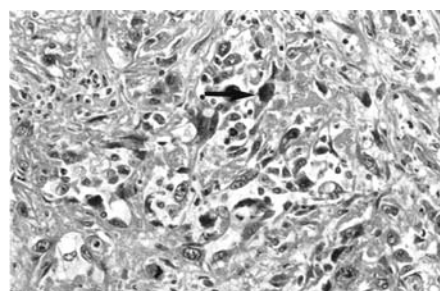


Figure 5. Angiosarcoma of the liver. Tumor cells show marked pleomorphism and nuclear hyperchromasia (e.g., arrow).

of arsenic from drinking water in human reproduction have not been adequately studied (1). To assess the potential effects of arsenic in human reproduction, a properly designed epidemiologic study in a sufficiently large population is necessary.

In conclusion, it is apparent that the health effects of arsenic are systemic in nature and may involve multiple organs. Epidemiologic studies confirm the relationship between chronic arsenic exposure and mortality from various cancers, especially those of the skin, lung, and bladder. We have presented in this article two case reports that further implicate arsenic as a causative agent in liver cancer. The biological mechanisms by which arsenic exerts its toxic and carcinogenic activities are not well understood at this time. To completely assess the potential adverse health risks of arsenic in various exposure situations, it is important to understand not only the mechanism(s) of action but also metabolic and toxicokinetic principles of arsenic activity. The search for biomarkers of exposure continues to be equally important as a means of identifying individuals susceptible to carcinogenesis. Establishing clear carcinogenic end points of arsenic exposure remains the overriding goal in determining intervention and preventing risks.

The cases presented here are from the ITTRCA and include a range of pathological conditions of the skin and liver that are related to arsenic exposure. Conditions in the skin include keratosis, hyperkeratosis, parakeratosis, pigmentation (hypopigmentation, hyperpigmentation), squamous cell carcinoma, and basal cell carcinoma. In addition to fibrosis, liver pathology includes hepatocellular carcinoma and angiosarcoma.

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