Merkel Cell Carcinoma in Patients with Long-Term Ingestion of Arsenic

Sheng-Yow Ho1,4, Yi-Chang Tsai2, Ming-Chin Lee3 and How-Ran Guo5

1Departments of Radiation Oncology, 2Pathology, and 3Plastic Surgery, Sin-Lau Christian Hospital, 4Institute of Basic Medical Sciences and 5Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Taiwan

Abstract: Merkel Cell Carcinoma in Patients with Long-Term Ingestion of Arsenic: Sheng-Yow Ho, et al. Departments of Radiation Oncology, Sin-Lau Christian Hospital, Taiwan—Merkel cell carcinoma (MCC) is a rare primary neuroendocrine carcinoma of the skin, mostly occurring late in life on sun-exposed body parts. Little is known about the specific etiological factors in the pathogenesis of MCC. A previous report indicated that arsenic exposure might cause MCC, which might be another specific type of skin cancer associated with arsenic exposure. On the southwest coast of Taiwan, high arsenic levels in artesian well water have been documented, and various diseases associated with arsenic exposure have been found to be prevalent in this area. We report two pathologically confirmed cases of MCC in patients who had histories of long-term ingestion of arsenic from drinking water. The tumors were on the anterior chest wall, an area less exposed to the sun, in both cases. The literature on the dose-response relationship between arsenic exposure and MCC is limited. We estimated that the total arsenic ingested by these two cases was around 14.7 and 2.6 gm, respectively. We also tried to assess the cancer risk on the basis of the estimated doses of arsenic exposure and the cancer risk model developed by the U.S. Environmental Protection Agency (EPA). The estimated lifetime target cancer risk was $1.3 \times 10^{-2}$ in Case 1 and $2.3 \times 10^{-3}$ in Case 2. Both are much higher than the $10^{-5}$ upper limit on lifetime cancer risk put forth by the U.S. EPA health protection standard. We believe that arsenic intoxication played an important role in the carcinogenic process of MCC in our cases. (J Occup Health 2005; 47: 188–192)

Key words: Merkel cell carcinoma, Skin cancer, Arsenic, Drinking water, Taiwan

Merkel cell carcinoma (MCC) is a rare primary neuroendocrine carcinoma of the skin, mostly occurring late in life on sun-exposed body parts. Little is known about specific etiological factors in the pathogenesis of MCC, but sun exposure and immunosuppression of various causes may play a role.

In 1991, Huang et al. reported three cases of MCC in Taiwan and found that one had concurrent chronic arsenicism with multiple Bowen’s disease and squamous cell carcinoma (SCC) of the skin, and that two were residents of an endemic area of chronic arsenicism on the southwest coast of Taiwan, generally known as the blackfoot disease endemic area (BFD area). MCC was reported with a suspected association with arsenic exposure in 1997, and then a case with definite arsenic exposure in a Japanese worker handling inorganic arsenic was reported in the following year. A study in Taiwan gathered 11 cases of MCC from two medical centers and found that 6 of the patients were residents of the BFD area. In this area, high arsenic levels in artesian well water have been documented for nearly half a century, and various diseases associated with arsenic exposure have been found to be prevalent. In particular, a peripheral vascular disease, known as “blackfoot disease” which may lead to gangrenous changes in the lower extremities, was noted. The BFD area consists of six hyper-endemic townships. The association between the consumption of artesian well water in this area and skin cancer has been documented since the 1960s, and the water from these wells contained high concentrations of arsenic, ranging from 0.01 to 3.0 ppm. Previous studies have documented a positive association between arsenic exposure and the occurrence of skin cancer in both men and women. A further analysis argued that the carcinogenicity of arsenic on the skin is cell-type specific.
because SCC and basal cell carcinoma (BCC) appear to be associated with the ingestion of arsenic, but such an association was not observed for malignant melanoma. Furthermore, a previous report suggested that arsenic exposure might cause MCC, which might be another specific type of skin cancer associated with arsenic exposure. We report two pathologically confirmed cases of MCC in patients who had histories of long-term ingestion of arsenic from drinking water. We also try to assess the cancer risk on the basis of the estimated amount of arsenic exposure and the cancer risk model developed by the U.S. Environmental Protection Agency (EPA).

Methods

The arsenic levels in the drinking water of the areas where the patients lived were assessed using data from a nationwide survey of wells conducted by the Taiwan Provincial Institute of Environmental Sanitation. The survey used the standard mercuric bromide stain method and published summaries of the measurements of 83,565 wells in 313 townships. We obtained detailed information on the residential history, clinical history, and occupation, and adopted the mean daily drinking water intake of 3.5 l by the male gender and 2 l by the female gender, which was estimated by Brown et al. Furthermore, we estimated the total arsenic intake from drinking water on the basis of the mean arsenic levels in drinking water measured in the residential townships as observed in the governmental survey.

The target cancer risk (TR) was estimated using the approach developed by the U.S. EPA, which uses the following model:

\[
TR = \frac{EF_r \times ED_{tot} \times MC \times CPSo}{BW_a \times AT_c} \times 10^{-3}
\]

where \(EF_r\) is the exposure frequency (350 d/yr), \(ED_{tot}\) is the exposure duration (yr), \(MC\) is the arsenic intake from the edible portion of food per day (\(\mu g/d\)), \(CPSo\) is the carcinogenic potency slope (1.5 per mg/kg-d for ingested inorganic arsenic), \(BW_a\) is the body weight (kg), and \(AT_c\) is the average lifetime (25,550 d=70 yr).

Case Histories

**Case 1**: A 55-yr-old male saltern worker with a red nodule on the anterior chest wall consulted the Department of Plastic Surgery of a teaching hospital in Tainan, Taiwan in December 2000. The tumor was 3 × 3 × 3 cm in size and about 3 cm away from the nipple laterally. No lymph node enlargement was palpated in the axillary or neck area, and he had no other systemic disease. He received a biopsy under the initial impression of a soft tissue mass, and the resected specimen was sent to the pathologist for diagnosis. A second operation, a wide excision and axillary lymph node dissection after the confirmation of MCC, was undertaken. No axillary lymph metastasis was pathologically found. The patient refused the suggested adjuvant treatment, but had regular follow-ups. No relapse was observed at his last follow-up in January 2004.

The resected specimen showed a circumscribed mass with an area of hemorrhage and necrosis in the dermis and subcutis (Fig. 1A). Microscopically, the mass was comprised of well-defined tumor cell nests separated by delicate fibrous septi (Fig. 1B). The nuclei of the tumor cells showed round to ovoid nuclei, finely dispersed granular chromatin, inconspicuous or small nucleoli, and frequent mitosis under the high power field (Fig. 1C). The tumor cells were diffusely immunoreactive for synaptophysin (neuroendocrine marker, Dako) (Fig. 1D). These findings are typical of MCC.

The patient was born in the Peimen Township, lived there for 47 yr, and then moved to the Hsuechia Township; both municipalities are in the Tainan County and within the BFD area. Among the 70 wells in Peimen that were included in the nationwide survey, 65 had an arsenic level above 0.05 ppm (equivalent to 50 \(\mu g/l\); the safety level at the time of the survey), and the arsenic levels ranged from undetectable (under 1 \(\mu g/l\)) to 2,500 \(\mu g/l\) (mean=600 \(\mu g/l\)). The patient used public well water in daily life, until a tap water system was constructed in Peimen in the 1960s. Therefore, he drank well water for a total of about 20 yr. The total arsenic ingested was around 14.7 gm (from birth to the installation of the tap water system in the 1960s), with a latency period of about 35 yr (mean arsenic level \([\mu g/l] \times 3.5 l/d \times 350 d \times [\text{years before the installation of tap water in their community}]\). We estimated that the mean arsenic exposure from drinking water of the case was 2,100 \(\mu g/d\) during the period when tap water was not available. The estimated lifetime TR was 1.3 × 10^{-2}.

**Case 2**: A 73-yr-old male farmer with a reddish nodule on the anterior chest wall consulted the Department of Surgery of the same hospital as Case 1, in December 2001. Tracing back the patient’s history, we found that he had verrucous papules that had gradually increased in number on the anterior chest, back, and extremities since the 1980s, which had been confirmed as multiple Bowen’s disease after biopsy in 1987. Multiple brownish patches and hyperkeratotic papules mixed with raindrop-like hypopigmentation on the chest wall were also observed (Fig. 2). Bowenoid actinic keratosis on the abdominal wall, multiple Bowen’s disease lesions in the trunk area, BCC (T1 lesion) in the scalp, and two SCC (T1 and T2 lesions) on the anterior chest wall were excised on different occasions from 1999 to 2000; all were skin lesions typical of chronic arsenic intoxication. The patient experienced an episode of ischemic stroke with the sequel of right hemiparesis in 1999, and he suffered from left
hydronephrosis due to a ureteral stone and underwent a left ureterolithotomy in 2000. He had no regular medical treatment for his hypertensive heart disease and had no smoking or drinking habit.

The MCC was a 2 cm reddish tumor with a sharp border, and the surface was partially eroded and easily bled (Fig. 2). The tumor was excised during the patient's visit in 2001, and the patient underwent a skin graft from the right inguinal region. Grossly, the tumor located in the dermis

**Fig. 1.** (A) The resected specimen showed a circumscribed mass with areas of hemorrhage and necrosis in the dermis and subcutis. (B) Micrograph of a section of the resected tumor specimen was comprised of well-defined tumor cell nests separated by delicate fibrous septi (original magnification × 100; scale bar 70 µm). (C) The nuclei of tumor cells showed round to ovoid nuclei, finely dispersed chromatin, inconspicuous or small nucleoli, and frequent mitosis under the high power field (original magnification × 400; scale bar 20 µm). (D) The tumor cells were diffusely immunoreactive for synaptophysin (neuroendocrine marker, Dako) (original magnification × 400; scale bar 20 µm).

**Fig. 2.** A dull red nodule about 2 cm with a sharp border was on the anterior chest wall. The surface was partially eroded and easily bled. Multiple brownish patches and hyperkeratotic papules mixed with raindrop-like hypopigmentation on chest wall were observed. Two skin graft scars were shown due to wide excision for squamous cell carcinoma previously.
and subcutis. Microscopically, the tumor area was infiltrated by mononuclear cells, which showed well-defined nests, solid sheets, and rosette-like arrangements. The neoplastic cells also had fine granular chromatin, scant to moderate amount of cytoplasm, and frequent mitotic figures, and they were immunoreactive for the neuroendocrine marker. These findings are typical of MCC. No regional lymph node enlargement or visceral metastasis was detected. Post-operative adjuvant radiotherapy was given, and no relapse was noted during follow-up visits. In March 2003, the patient expired due to congestive heart failure.

The patient was born and lived in the coastal An-Nan District of Tainan City near the BFD area for his entire life. Among the 495 wells in his residential area that were included in the nationwide survey, 85 had an arsenic level above 50 \( \mu g/l \), and the arsenic levels ranged from undetectable to 3,000 \( \mu g/l \) (mean=60 \( \mu g/l \)). He also used public well water in his daily life until a tap water system was constructed in the district in the 1960s; therefore, he drank well water for a total of about 35 yr. The patient was involved in farming, mostly rice, but could not recall the use of herbicides or insecticides containing arsenic. We estimated that the total arsenic ingested was around 2.6 gm (from birth to the installation of a tap water system in the 1960s), with an exposure duration of about 35 yr. We estimated that the mean arsenic exposure from drinking water of the patient was 210 \( \mu g/d \) during the period when tap water was not available. The TR for this patient was 2.3 \( \times 10^{-3} \).

No immunosuppressive therapy was prescribed in either case, and written informed consents for the treatment and examinations were obtained from both patients.

**Discussion**

MCC is a rare primary cutaneous neoplasm that affects mostly the elderly population. Most studies show a male predominance (ratio approximately 2 to 3:1), with an average age of 60 to 70 yr at the time of diagnosis. Several names have been used in the past to describe this tumor, such as “primary neuroendocrine carcinoma of the skin” and “cutaneous APUDoma,” reflecting the neuroendocrine origin of the cells. The term “primary small cell carcinoma of the skin” reflects its resemblance to small cell lung carcinoma, whereas “undifferentiated or anaplastic carcinoma of the skin” and “trabecular carcinoma” reflect some of its histologic features. The term “Merkel cell carcinoma” is used because of the presumed origin from the Merkel cells of the skin. At the time of diagnosis, patients typically present with a solitary cutaneous nodule that has grown rapidly over a few weeks to months and may ulcerate. The tumor behavior of MCC is aggressive and carries a poor prognosis. About 75% of patients present with localized disease at first, but 30% develop local or systemic recurrence during follow-ups. Most series have suggested that adjuvant radiotherapy could improve local control, but patients are still at high risk for distant metastasis. The tumor frequently spreads systemically, and common secondary sites include the skin, lymph nodes, liver, lung, bones, and brain.

A large review of 1,024 cases found MCC affects primarily the sun-exposed areas of the skin, with approximately 41% on the face and neck; 33% appear on the extremities, and only 20% on less sun-exposed areas such as the trunk. The tumors of our two patients were on the less sun-exposed areas. When our 2 patients are added to the 11 patients from a previous report in Taiwan, there have been a total of 8 patients from the BFD endemic area, 4 (50%) of whom had lesions in a less sun-exposed area, including three on the chest wall and one on the abdominal wall. In contrast, the cases from outside the BFD area all had lesions in sun-exposed areas, including the head and extremities. Therefore, the distribution of such skin lesions in less sun-exposed areas might be indicative of arsenic exposures.

Arsenic poisoning can cause systemic effects and may result from environmental, occupational, or medical exposure. Long-term exposure to inorganic arsenic can lead to the development of visceral malignant tumors in the skin, lung, urinary tract, and liver. The reported cases of MCC due to chronic arsenic intoxication in the literature were discovered in Taiwan and Japan in the 1990s, and six cases from the BFD area were reported in Taiwan thereafter. Among the inhabitants of the BFD area, a remarkable number of chronic arsenicism cases manifesting as hyperpigmentation, keratosis, and cancers have been observed. Arsenical skin cancers include Bowen’s disease, BCC, SCC, and their various combinations. Our second case had typical chronic arsenicism with presentations of arsenic keratosis, multiple Bowen’s disease, BCC, and SCC. The coexistence of MCC and SCC has been reported in the literature, but the relationship between these tumors has not been extensively elucidated. MCC occurring in our patients, who had chronic arsenicism, indicates that arsenic is a carcinogen that may lead to MCC in addition to SCC, BCC, and Bowen’s disease, by acting on different progenitor cells. A previous study in Taiwan showed that SCC and BCC appear to be associated with the ingestion of arsenic and that such an association was not observed for malignant melanoma, which leads to the conclusion that the carcinogenicity of arsenic on skin is cell-type specific. Another report from Taiwan collected 11 cases of MCC from two medical centers, and found that 6 of the patients had chronic arsenicism. Therefore, arsenic intoxication may have played an important role in the carcinogenic process of MCC in our cases.

We estimated that the mean arsenic exposure from drinking water of these two cases was 2,100 and 210 \( \mu g/l \).
d, respectively, during the period when tap water was not available. The latency between the development of skin cancer after environmental or occupational exposure was 12 to 45 yr in one report\(^{13}\), and the two cases presented herein developed the disease within that range. We have reported a case of a patient with hepatic angiosarcoma with long-term ingestion of arsenic in the vicinity of the BFD area, and by the same approach, the mean exposure to arsenic from drinking water was estimated to be 120 µg/d\(^{16}\). A recent study in Taiwan showed increased risks of several types of cancer in villages with a median arsenic level in well water below 50 µg/l\(^{21}\), which was the previous maximum contaminant level (MCL), and the U.S. EPA has lowered the MCL to 10 µg/l\(^{22}\). In our cases, before the installation of tap water systems, the exposure levels were much higher than the MCL. According to the U.S. EPA model for the carcinogenic effect of inorganic arsenic, the estimated lifetime target cancer risks in our two cases were 1.3 × 10\(^{-6}\) and 2.3 × 10\(^{-6}\), which is much higher than the 10\(^{-6}\) upper limit set by the health protection standard of the U.S. EPA\(^{23}\). Therefore, it is plausible that arsenic intoxication played an important role in the carcinogenic process of MCC in our cases.

The annual incidence of MCC in the U.S. was estimated as 0.23 cases per 100,000 for whites, but only 0.01 cases per 100,000 for blacks\(^{11}\). The reported cases of MCC among Taiwanese are very limited, and no estimate of incidence can be found in the literature. Therefore, further epidemiological studies on MCC in Taiwan are warranted to draw a clearer picture of MCC among Taiwanese and to explore further the association between MCC and arsenic intoxication.

Acknowledgments: This study was supported by the Sin-Lau Christian Hospital and the National Science Council of Taiwan, R.O.C. (Grant NSC93-2320-B-006-031).

References
21) Environmental Protection Agency: National primary drinking water regulations; Arsenic and clarifications to compliance and new source contaminants monitoring; Final rule. Fed Reg 66, 6976 (2001)