台灣西南沿海地區慢性砷中毒的皮膚病變—臨床病理研究

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目標：慢性砷中毒是台灣西南沿海重要的地區性流行病，本研究的目的在分析到一教學醫院診治的慢性砷中毒病人的皮膚表現及鱗狀細胞癌(SCC)病理變化與預後的關係。**方法**：此爲一回溯性的研究，收集了1988年6月至1996年5月間在成大醫院皮膚科診斷爲慢性砷中毒的病例共303人。**結果**：病人包括170男性，133女性，年紀爲29-90歲(平均63.4歲)。其中3人有烏腳病，62.4%病例有砷黑色素症 (rain-drop sign)，72.6%有手掌或足蹠點狀或瀰漫性角化，94%有至少一個皮膚癌，絕大多數爲波汶氏病(BD)。大多數皮膚癌分佈在軀幹及四肢。我們對234病人的代表性或較嚴重的皮膚癌病灶作了切片或切除，共檢查了311病灶，其病理診斷分別爲BD 58%，SCC 20%，基底細胞癌21%，及少數其他惡性腫瘤包括2例Merkel細胞癌。有1/4 的SCC病灶合併BD。SCC有25%來自軀幹，56%來自四肢，其中手及足部佔46%。SCC病人中23% 發生淋巴結或遠處轉移，其原發SCC皆位於手足或頭皮，這些部位的SCC有偏高的轉移率 (38%) 及死亡率 (24%)，預後最差。少數病人合併其他器官癌症，包括移行上皮細胞癌18例、肺癌12例、肝癌5例。我們分析SCC病理變化與預後的關係，發現分化不良者較有轉移之危險性，但就頭皮及手部良好及中等分化的SCC而言，其危險因子爲腫瘤厚度大於6公厘，侵犯深部眞皮層及浸潤性的型態。**結論**：本研究有關慢性砷中毒的各種皮膚變化及砷SCC的預後與文獻者大致相近，但與非砷SCC相比，砷SCC較多爲分化不良；發生於頭皮及手足的砷SCC，較多導致轉移及死亡，應儘早切除。(中華衛誌 1999；**18**(附冊 **1**)：97-109)

關鍵詞：慢性砷中毒、流行病、砷癌、皮膚。

Cutaneous manifestation of chronic arsenism in patients from the southwestern coast of Taiwan: A Clinicopathologic Study

Objectives: The purpose of the study was to review the cutaneous manifestation, pathologic classification and the metastatic and mortality rates of arsenical skin cancers from a hospital-based patient population. **Methods**: A retrospective study of 303 cases of chronic arsenism from the endemic areas diagnosed in National Cheng-Kung University Hospital from June 1988 to May 1996 were analyzed. **Results**: The patients consisted 170 men and 133 women, aged from 29 to 90 years (mean 63.4 years). Three patients also had BFD. The incidence of arsenic melanosis or rain-drop sign, punctate keratosis of palms or/and soles, and skin cancers was 62.4%, 72.6% and 94%, respectively. Most arsenical skin cancers were Bowen's disease and mainly occurred on the trunk and extremities. A total of 311 representative or more advanced skin tumors were biopsied or excised from 234 patients; histopathologically 58% were Bowen's disease, 20% squamous cell carcinoma (SCC), 21% basal cell carcinoma (BCC), and a few other malignancies including 2 Merkel cell carcinoma. Of the SCCs, 25% arose in Bowen's disease. The SCCs were mainly located on the trunk (28%), and extremities (56%), especially the hands and feet (46%). Lymph node or visceral metastasis developed in 13 (23%) of the patients with SCC; in each case, the primary SCC was located at the acral parts or scalp. This subgroup had a high metastatic rate of 38% and mortality rate of 24%. Regarding the associated internal malignancy, 16 patients had transitional cell carcinoma (TCC), 10 had lung cancer, 5 had hepatoma and 2 had TCC and lung cancer. Based on analysis of the histologic parameters of arsenical SCCs, poor differentiation was a risk factor for metastasis in SCCs from all sites; in the well or moderately-well differentiated SCCs from the hand and scalp, the risk factors were deep dermal invasion, tumor thickness>6mm and infiltrating pattern. **Conclusions**: The cutaneous manifestation of chronic arsenism and the metastatic and mortality rates of arsenical SCCs of our series were comparable to the results reported previously. Compared with non-arsenical SCCs, higher proportion of arsenical SCCs were poorly differentiated. Furthermore, arsenical SCC of the hands, feet and scalp were more aggressive and should be completely excised as early as possible. *(Chin J Public Health. (Taipei): 1999;**18(suppl 1)**:97-109)*

Key words: chronic arsenism, endemic, arsenical carcinoma, skin.

INTRODUCTION

Chronic arsenism caused by chronic exposure to inorganic arsenic from medicinal, environmental and occupational [1-9] have been well documented. Typical cutaneous manifestation of chronic arsenism consists of (1) arsenical melanosis characterized by diffuse bronze pigmentation, most intense on the trunk, with macular areas of depigmentation, producing a distinctive "rain-drop" appearance, (2) arsenical keratosis with punctate or corn-like keratotic lesions characterically affecting the palms and soles; and (3) multiple skin cancers, including Bowen's disease, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Most arsenical skin cancers are located on the non-sun-exposed areas, in contrast to ordinary skin cancers, which are primarily UV-induced and distributed on the head, neck and dorsal aspect of the hands. In addition to skin cancers, there is an increased incidence of internal malignancies in patients with chronic arsenism [10].

In a limited region of the southwest coast of Taiwan (mainly in Tainan county, Tainan city and Chai-Yi county) artesian well water with high concentrations of arsenic (ranged from 0.35 to 1.34 ppm with a median of 0.78 ppm) had been used for more than 50 years. There was high prevalence of chronic arsenism and black-foot disease (BFD), a unique peripheral vascular insufficiency resulting in progressive gangrene of the extremities [5,6,10-14]. In 1963, a prevalence rate of arsenic intoxication to be 37.17% (86.64% in persons above 50 years of age)[15]. In another survey of 40421 residents, the prevalence of hyperpigmentation, hyperkeratosis and skin cancer in the endemic area in 1965 to be 183.5‰ 71.0‰and 10.6‰, respectively with the corresponding shortest latent period to be 3 years, 14 years and 24 years [5]. In a series of 428 patients with arsenical skin cancers, the incidence of rain-drop sign and keratosis was 90% and 72%, respectively [5]. A dose-response relationship has been observed between the occurrence of skin cancer and the arsenic concentrations in the artesian water [5,10,16-18].

These earlier studies were epidemiological investigations in which the cutaneous lesions were examined during field surveys more than 20 years ago. Our hospital, the only medical center in this endemic area, was founded in 1988. Since then, we have seen more than 300 patients with chronic arsenism. The purpose of this report is to give a clinical and pathologic description of these patients from the clinical perspectives and to bring attention to the high mortality rate of arsenical SCC arising from the hands, feet and scalp.

PATIENTS AND METHODS

The subjects in this retrospective, hospital-based study included all patients with a diagnosis of chronic arsenism made in the Department of Dermatology, National Cheng-Kung University Hospital, between June 1988 and May 1996. A total of 303 patients were retrieved from the medical records. Most patients came to our clinics by self-referral for their skin tumors. A small proportion of the patients was seen at consultations or for other unrelated dermatological conditions. The majority of the patients were evaluated and treated on an outpatient basis. The skin lesions were recorded on diagrams or by photography. The clinical criteria for diagnosing chronic arsenism consisted of history of arsenical exposure, specifically drinking arsenic-contaminated artesian well water from the endemic area, plus two of the following characteristic cutaneous findings: (1) mottled hyper- and hypopigmentation (rain-drop sign), (2) punctate hyperkeratosis of palms or/and sole, and (3) skin cancer(s), especially multiple Bowen's disease. In addition to the physical examination, laboratory investigations including chest X-ray, ab-

dominal sonography, urine cytology, tumor markers (alpha fetal protein, carcinoembryonic antigen) and cell mediated immunity were performed in some patients.

The clinical data, including age, sex, place of birth and residency, medical history of prior or concurrent malignancy and peripheral vascular disease, clinical findings, treatments and outcome were reviewed from medical records. In 234 patients, one or more selected skin tumors, usually the representative or the more advanced lesions, were biopsied or excised. The histopathologic findings of SCCs, including degree of differentiation, maximal thickness of the neoplasm, depth of invasion, presence of infiltrating pattern or vascular involvement were also analyzed. The differentiation of SCCs was graded according to the World Health Organization criteria: Grade I - well differentiated; Grade II - moderately well differentiated; and Grade III - poorly differentiated. For comparison, the SCCs from the non-arsenism patients diagnosed during the same study period were also reviewed.

RESULTS

Of the 303 patients, 170 were men and 133 were women. The mean age at the time of diagnosis was 63.4 years (range, 29-90 years) (Table 1). Seventy-nine percent of the patients were residents from Shuehchia, Beimen, Anting, Putai, Yichu and Annan. The duration of the skin cancers was said to vary from several months to more than 10 years. However, it was a rough estimation as the majority of our patients was old and could not remember the exact duration. Furthermore there were usually multiple skin lesions in each patients. About 45% of the patients came for treatment after the lesions had been noticed for more than 2 years.

Rain-drop sign was recorded in 189 (62.4%) patients, punctate or diffuse keratosis of palms or/and soles in 220 (72.6%) patients (Table 2), and SCC in-situ (Bowen's disease) or/and SCC, or/and BCC in 284 (93.7%) patients. The real incidences of rain-drop sign and keratosis of palms or/and soles might be higher, because this was a retrospective study, the recording of these signs might be incomplete in some patients. The corresponding figures were 79% and 75% in a small group of 24 patients whom were seen more recently and their cutaneous findings were recorded completely. The rain-drop sign (Fig. 1) was most commonly observed on the back, chest, buttocks, thighs and arms. Punctate keratosis (Fig. 2) was usually more prominent on the soles than on the palms. Diffuse keratosis was observed on the soles in some patients. It was characterized by diffuse hyperkeratosis with slight unevenness of the surface caused by numerous small, shallow depression, or coalescence of tiny, pinhead-sized keratosis (Fig. 2)

The numbers of skin cancers in individual patients varied from 1 to 94. About 94% of the patients with skin cancers had multiple cancers, mostly more than 10 lesions. The skin cancers mainly occurred on the trunk and extremities (Fig. 3). The great majority of them were Bowen's disease, which was characterized by well-demarcated erythematous, eroded or crusted plaque. The lesions were typically thin, but some were fairly thick, nodular or even fungating. In

Table 1. Age and Sex Distribution of 303 Patients with Chronic Arsenism (June 1988 to May 1996)

	< 30	30-39	40-49	50-59	60-69	70-79	80-89	90-99	Average
Male	0	4	14	47	59	40	5	1	62.93
Female	1	2	4	36	47	36	7	0	64.09
Total	1	6	18	83	106	76	12	1	

Table 2. The Percentage of Characteristic Skin Lesions in 303 Patients with Chronic Arsenism

	Punctate keratosis (palms or/and soles)	Rain-drop sign
Positive	72.6% (220/303)	62.4% (189/303)
Negative	8.2% (25/303)	18.5% (56/303)
No record	19.1% (58/303)	19.1% (58/303)

Table 3. Pathologic Diagnosis of 311 Skin Cancers in 234 Patients with Chronic Arsenism (1988-1996 NCKUH)

Types	Cases no
BD	117
SCC	28
BCC	39
BD+SCC	25
BD+BCC	15
BD+SCC+BCC	4
BD+adenoca	3
BD+Merkel cell ca	2
BD+MM	1

BD: Bowen's disease; SCC:squamous cell carcinoma; BCC: basal cell carcinom; MM: malignant melanoma

addition to Bowen's disease and SCC, BCCs were also frequently observed. They consisted of papules, nodules or thin plaques. Most BCCs were blackish. A total of 311 specimens from 234 patients were examined. Based on the pathologic diagnoses, 58% were Bowen's disease, 20% were SCC, 21% were BCC (mostly pigmented type). Ten patients (4.3%) had other types of skin cancers including keratoacanthoma, malignant melanoma, Merkel cell carcinoma (Table 3). Four lesions of punctate keratosis of the palm or sole were examined; none showed cellular atypia.

A total of 100 patients (57 arsenism and 43 non-arsenism patients) with primary cutaneous SCC had been diagnosed in our department during the same study period. The primary sites of the SCC in the arsenism group were mainly on the trunk (27.9%) and extremities (55.7%), especially the hands and feet (45.9%) (Fig. 4). Sixty-nine percent of the arsenical SCCs occurred on the non-sun-exposed skin, while 81.4% of the SCCs in the non-arsenism group located on the sun-exposed areas (Table 4). Fifteen out of 61 arsenical SCCs (24.6%) arose in the lesions of Bowen's disease while only 2 out of the 43 non-arsenical SCCs did so.

Most of the thin Bowen's lesions were treated by liquid nitrogen cryotherapy or 5-fluorouracil cream. The SCCs, thick Bowen's disease and BCCs, . The patients were followed periodically up to 8 years, average 4 years. Among the patients with SCCs, metastasis to regional lymph nodes developed in 13 (22.8%) patients in arsenism group (Table 5). Their primary lesions were all located on the acral parts and scalp. Nine of them also had distant metastasis to the lung, skin, bone, brain, liver, or adrenal gland (Table 6), and 8 of them died of the disease. Three patients (6.7%) from the non-arsenism group developed metastasis to the regional lymph node, but there was no disease-related mortality. Regarding the associated internal malignancy, 16 patients with arsenism had transitional cell carcinoma (TCC), 10 had lung cancer, and 5 had hepatoma (Table 7). Two patients had TCC, lung cancer and skin SCC.

In the present study, the distribution of well, moderately-well and poorly differentiated SCCs were 15.1%, 56.6%, 28.3%, respectively in the arsenism group, while the corresponding figures were 39.5%, 55.3% and 5.3% in the non-arsenism group.

DISCUSSION

The mean age in our series of 303 patients with chronic arsenism was 63.4 years. Only 7 patients were younger than 40 years of age. Since tap water was supplied around 1960-1970

to the endemic area, they drank the artesian well water for less than 20 years. All of them had punctate keratosis, but only 6 had rain-drop sign, and 3 had arsenical skin cancers. Of the 3 patients with cancers, one was a 34-year-old man who had 7 pigmented BCCs on the back, scalp and calf. His sister, a 29-year-old woman (the youngest patient with skin cancer in our series) had a pigmented BCC on the scalp. The last one was a 39-year-old man, with a SCC arising in a lesion of Bowen's disease on the abdomen. The duration of arsenical exposure in these 3 patients was 16, 15, 12 years, respectively.

Arsenical melanosis or the rain-drop sign occurs mainly on the trunk, buttocks and thighs. The rain-drop appearance was imparted by numerous small, hypo- or depigmented macules about 0.2 to 0.4 cm in size in a background of bronze discoloration (Fig. 1) which was sometimes mixed with diffuse dappling of dark brown macules or maculopapules (Fig. 5). The hypopigmented macules tended to be poorly demar-

Table 4. The Primary Location of 100 Patients with Squamous Cell Carcinoma

	Chronic arsenism			Non-arsenism		
	M	F	%	M	F	%
Face	3	0	4.9	8	16	55.8
Scalp	3	3	9.8	1	1	4.7
Lip	1	0	1.6	6	0	13.9
Trunk			27.9			4.7
Chest	3	1		1	0	
Abdomen	3	6		0	0	
Back	1	1		1	0	
Buttock	2	0		0	0	
Extremities			55.7			20.9
Upper limbs	0	2		0	1	
Lower limbs	2	2		2	1	
Hand	6	13		2	2	
Foot	1	8		1	0	
Total*	25	36		22	21	

* Four arsenism patients had 2 lesions

Table 5. Metastatic Rate According to Location of Squamous Cell Carcinoma

Location	Chronic arsenism	Non-arsenism
Scalp	2/6 (33.3%)	0/2
Face	0/3	1/24 (4.2%)
Lip	0/1	0/6
Trunk	0/17	1/2 (50%)
Extremities (except hand & foot)	0/6	0/4
Hand	7/19 (36.8%)	1/4 (25.0%)
Foot	4/9 (44.4%)	0/1

Table 6. The Sites of Metastasis in Patients with Squamous Cell Carcinoma

	Chronic arsenism (n=57)	Non-arsenism (n=43)
Regional lymph node	13	3
Distant lymph node	2	0
Extranodal sites		0
Lung	5	0
Skin	4	0
Bone	4	0
Brain	2	0
Liver	1	0
Adrenal gland	1	0
Total metastasis cases	13 (23%)	3 (7.0%)

Table 7. Associated Internal Malignancy in 303 Patients with Chronic Arsenism (1988-1996 NCKUH)

Malignancy	Cases no.
Bladder TCC	16 (5.3%)
Lung ca	10 (3.3%)
Hepatoma	5
Melanoma	1
Multiple myeloma	1
Prostate ca	1
Nasal ca	1
Gastric ca	1
Colon ca	1

Table 8. Cutaneous Manifestation of Chronic Arsenism

	Tseng et al (1968) (n=428)	NCKUH (1997) (n=303)	NCKUH* (n=24)
Melanosis	90%	62.4%	79%
Keratosis	72%	72.6%	75%
As cancer	100%	93.7%	
Multiple cancer	99.5%	94.0%	

* In a study on a small group of 24 arsenism patients

Table 9. Metastasis and Mortality of SCC of the Skin

	Yeh & How (1968)	Yeh (1973)	NCKUH (1997)	Epstein et al.* (1968)	Sedlin** (1963)
Metastatic rate	15%		22.8%	2-3.3%	20-30%
Mortality		14.7%	14.0%		

* Primary cutaneous squamous cell carcinoma[21]

** Squamous cell carcinoma arising in association with chronic osteomyelitis

Table 10. Histopathologic Classification of SCC

Yeh (1963)			NCKUH (1997) (Arsenism)	NCKUH (1997) (Non-arsenism)
I	4.8%	Well diff.	15.1%	39.5%
II	21.7%	Moderate well diff.	56.6%	55.3%
III	65.2%			
IV	8.7%	Poorly diff.	28.3%	5.3%

cated, but the depigmented macules were sharply demarcated and were indistinguishable from idiopathic guttate hypomelanosis (Fig. 6). Although the rain-drop sign was stated to be more marked on the unexposed skin surface [15], in some of our patients, it was less discernible on the buttocks and upper thighs (Fig. 7), indicating that suntan enhanced the contrast of hypo- and hyper-pigmentation of the raindrop sign in the light skin individuals. This sign was found in 90% of the 428 patients with skin cancers [5]. The incidence was lower in our series (Table 8). It might be attributed partially to lightening of the melanosis over time after discontinuation of arsenical exposure, a phenomenon noted by Hamada & Horiguchi [19].

Arsenical keratosis is a precancerous condition manifested by multiple horny growth, usually the palms and soles, which may progress to SCC. Arsenical keratosis of the palms and soles may be papulonodular (punctate keratosis), diffuse or combined [15]. The papulonodular type is well recognized and regarded as a pathognomic finding of chronic arsenical poisoning. Although less well known, the diffuse type was fairly common in our series, especially on the soles. It may be overlooked as hyperkeratosis secondary to friction because many patients worked in the farm or salt field barefooted, or misdiagnosed for desquamative dermatophytosis.

In addition to the palmoplantar lesions, arsenical keratosis also manifested as multiple small, usually only a few millimeter, reddish brown, scaly papules on other parts of the body, mostly on the trunk (Fig. 8). Such lesions probably were early, evolving lesions of Bowen's disease, but only a few of them had been examined and confirmed pathologically. This type of

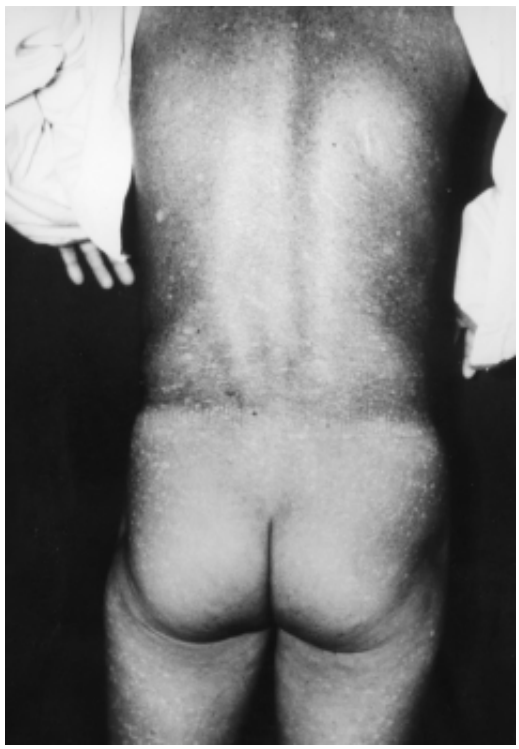

Fig. 1. Rain-Drop Sign in Chronic Arsenism. Diffuse bronze-colored hyperpigmentation with numerous hypopigmented macules on the back, buttocks and thighs, imparting a "rain drop" appearance which was accentuated by suntan on the back.

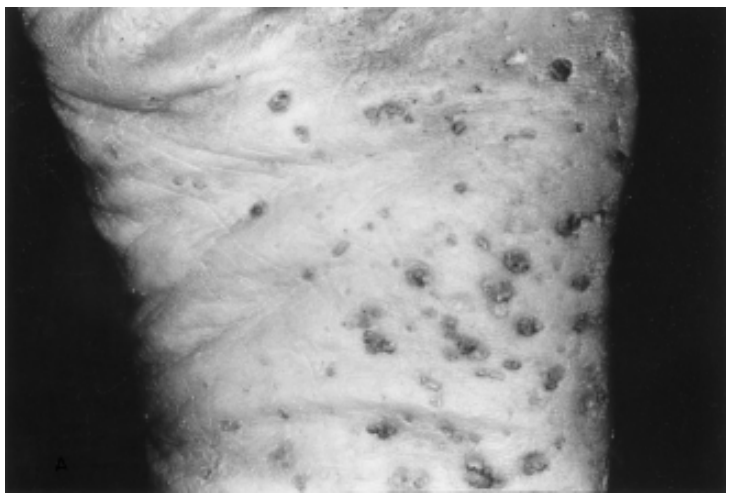

Fig. 2A. Punctate or Diffuse Palmoplantar Hyperkeratosis in Chronic Arsenism. Typical lesions are discrete, pinhead to 4 mm-sized, punctate keratotic papules.

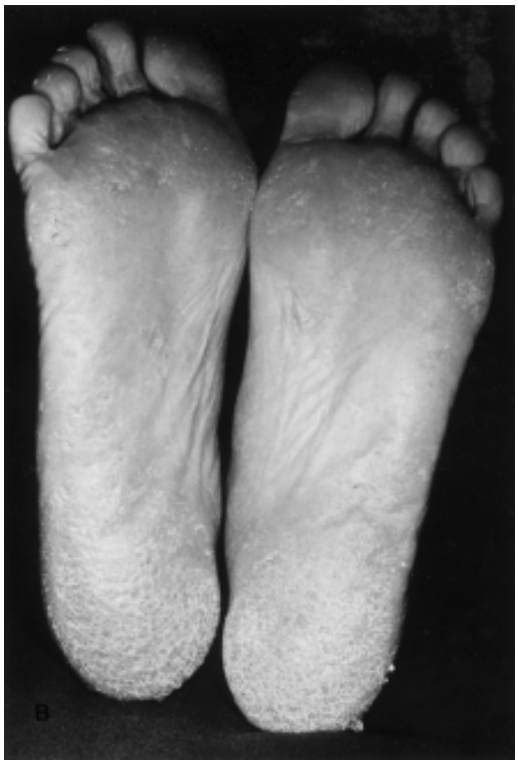

Fig. 2B. The diffuse type shows diffuse hyperkeratosis mainly on the heels with numerous small depressions or confluence of tiny punctate keratosis. Note small discrete punctate lesions on the metatarsal area.

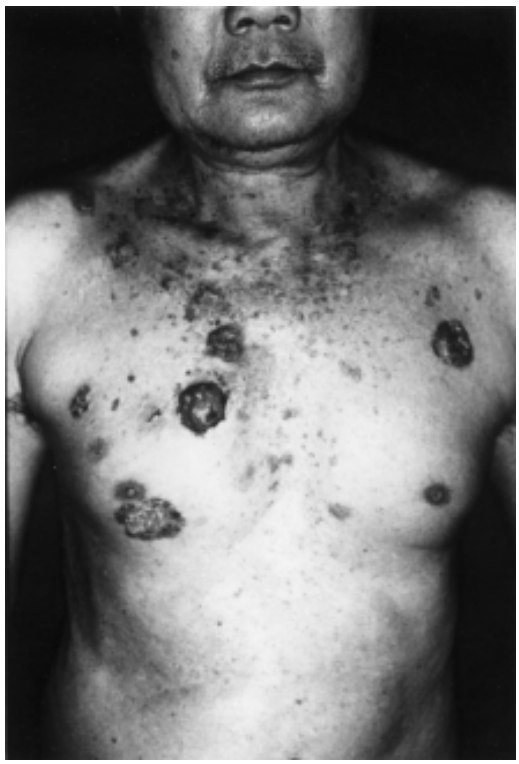

Fig. 3. Arsenical Skin Cancers. Many lesions of Bowen's disease or squamous cell carcinoma are present on the chest and V of the neck, sparing the face. Note the raindrop sign is inapparent in this patient who had fair skin without suntan.

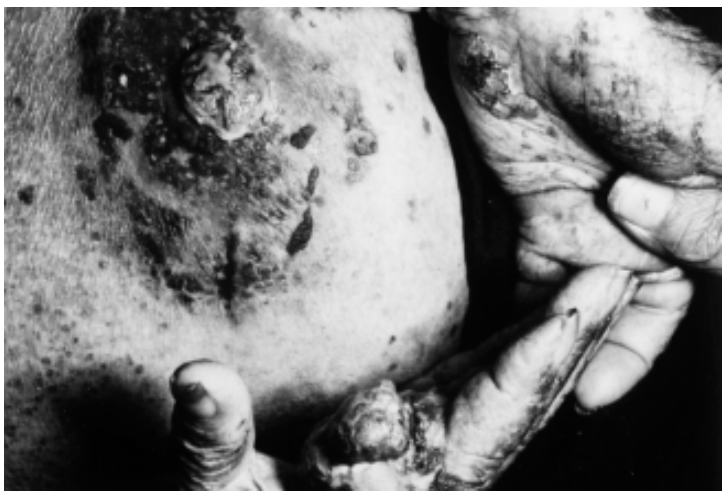

Fig. 4. Arsenical Skin Cancers Two squamous cell carcinoma on the abdomen and on the stump of right index finger. Note the punctate keratosis and a Bowen's disease on the left palm.

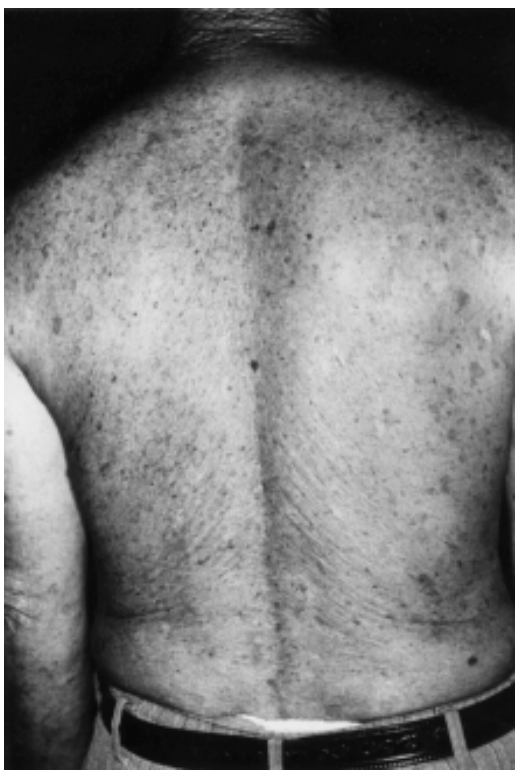

Fig. 5. Rain-Drop Sign in Chronic Arsenism. On a background of brownish hyperpigmentation and small hypopigmented macules, there is diffuse dappling of small dark brown macules or maculopapules.

lesions should be distinguished clinically from solar lentigo, seborrheic keratosis and solar (actinic) keratosis, which were frequently observed in our patients (Fig. 6,9).

Pathological findings of arsenical keratosis vary from benign-looking hyperplasia through mild or moderate atypia to frank Bowen's disease [20]. Similar spectrum was observed in a study of 67 lesions of arsenical keratosis from all body sites, including 5 from the palm or sole [15]. However, the majority in that series showed no atypia of the lesions. In our series, we have only examined 4 lesions of arsenical punctate keratosis of the palm or sole; none of them displayed atypia. We also sampled a few small keratotic papules of evolving lesions of Bowen's disease outside the palms & soles in the individuals without more advanced lesions of Bowen's disease. Pathologically, they displayed proliferation of atypical keratinocytes involving the lower part of the epidermis only.

The majority (69%) of the arsenical skin cancers in the present study involved the non-sun-exposed skin; similar to the 74.5% [5]. The proportion of Bowen's disease, SCCs and BCCs in the present study was 56.9%, 19.6% and

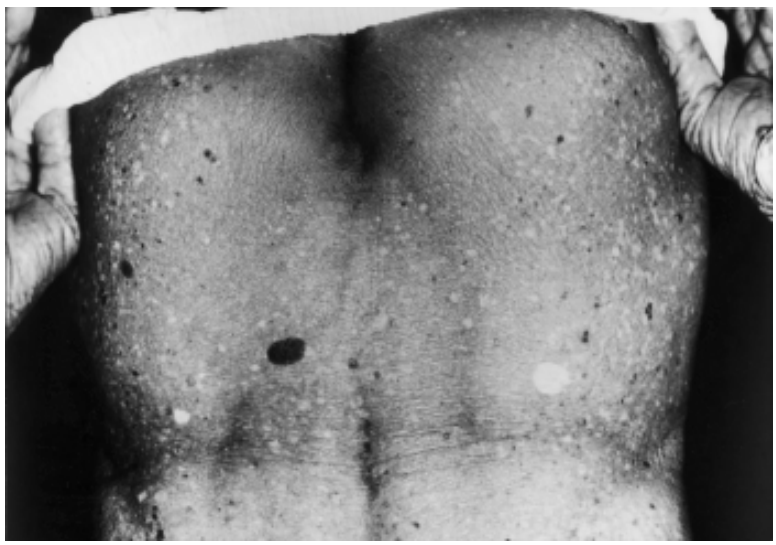

Fig. 6. Rain-Drop Sign in Chronic Arsenism. Numerous sharply demarcated, depigmented macules stand out on a background hyperpigmentation. Note the presence of many dark brown lesions of seborrheic keratosis.

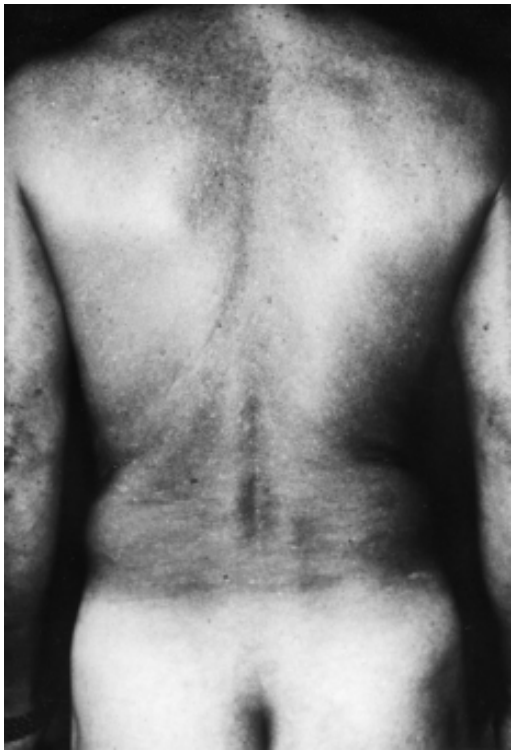

Fig. 7. Rain-Drop Sign in Chronic Arsenism. Though rain-drop sign typically is more prominent on the sun-protected sites, it is less discernible on the buttocks of a light skin-colored patient without suntan.

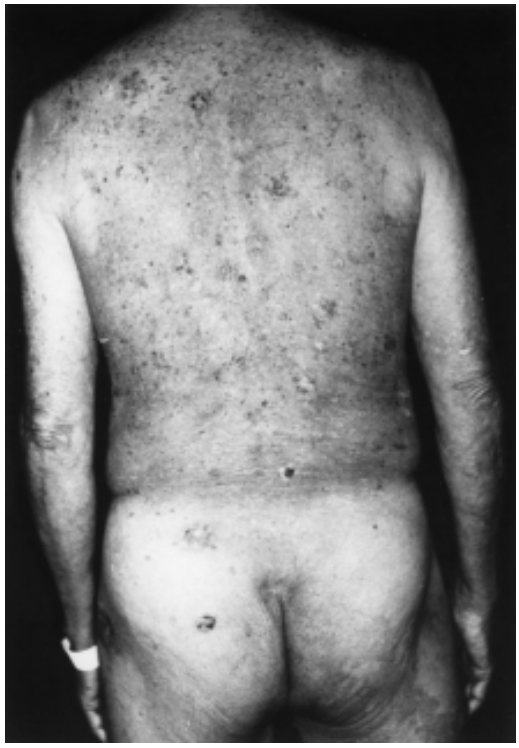

Fig. 8. Arsenic Keratosis on the Non-Acral Areas. In addition to several larger lesions of Bowen's disease, there are numerous small reddish brown crusted or keratotic papules which are most likely evolving lesions of Bowen's disease.

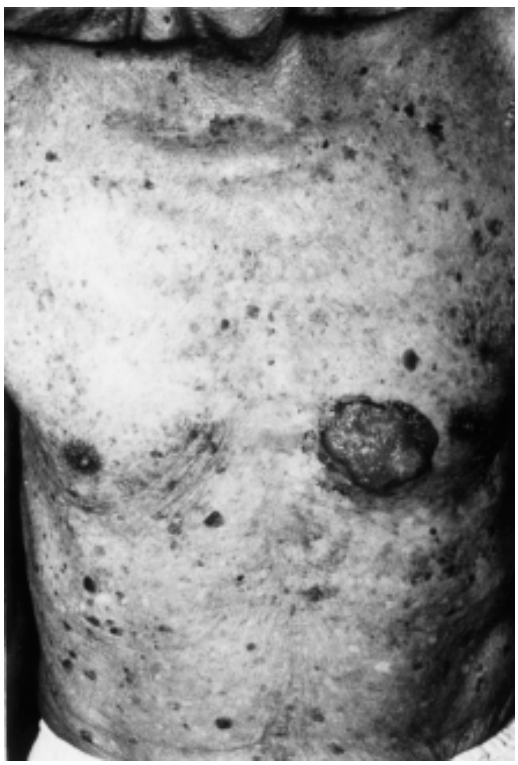

Fig. 9. Seborrheic Keratosis in Chronic Arsenism. In addition to a fungating squamous cell carcinoma, there are many dark brown papules and nodules of seborrheic keratosis on the trunk.

21.5%, respectively. The corresponding figures were 58%, 18.8%, 14.8% in a series of 303 skin cancers [6]. These figures, of course, did not reflect the real proportion of arsenical carcinomas, since all SCCs and most BCCs were biopsied or excised while usually only the representative or advanced lesions of Bowen's disease were examined pathologically. Our estimation is that more than 80% of the arsenical cancers were Bowen's disease. Twenty-five percents of the SCCs in the present series developed in the preexisting Bowen's disease, a finding similar to that reported [15].

The metastatic rate of primary cutaneous SCC is approximately 2 to 3.3% [21,22]. It is more likely to develop in carcinomas arising from antecedent lesions of chronic ulcers, burns scars, arsenical keratosis, x-ray injury. The metastatic rate of arsenical SCC was 33% [23] and 15% [24]. It was 22.8% (13/57) in the present study (Table 9). The relatively high metastatic rate was probably due to a higher proportion of SCCs involving hands and feet (46%) in our series, which was associated with a metastatic rate of 39% as a subgroup. An analysis of the cause of death among the 174 patients with arsenical skin cancer up to 1971 by Yeh revealed that 33.3% died of carcinoma of various sites, including 14.7% died of skin cancer [6]. In the present study, 8 of the 57 (14.0%) arsenism patients with SCC of the skin died of metastatic disease.

It is worth noting that, all metastases in our series arose from acral and scalp SCCs. These cancers had a fairly high metastatic rate of 38% and mortality rate of 24% as a group. The aggressive behavior could be partially attributed to the fact that the treatment in these cases tended to be delayed or incomplete. Often patients were reluctant to have biopsy or complete excision performed on the tumors of the hands or feet. Many lesions were treated incompletely by electrodessication or cryotherapy with liquid nitrogen before they received a final diagnosis or excision. The delayed and inadequate treatments apparently contributed to the poor outcome in such patients. Based on this experience, we recommend that the SCC on the hand, foot and scalp should be treated by complete excision as early as possible.

Analysis of the histology parameters of arsenical SCCs of the present series revealed that poor differentiation was a risk factor for metastasis in the SCCs from all sites. However, in the well or moderately well differentiated SCCs from the scalp and hands, the risk factors were deep tumor invasion, tumor thickness > 6 mm and infiltrating pattern. In a study the SCCs were classified grade I to IV according to Broder' classification, the proportion of each grade was 4.8%,

21.7%, 65.2% and 8.7%, respectively [13]. The distribution was said to be about the same as in ordinary SCCs. In the present study, the distribution of well, moderately-well and poorly differentiated SCCs were 15.1%, 56.6%, 28.3%, respectively in the arsenism group, while the corresponding figures were 39.5%, 55.3% and 5.3% in the non-arsenism group (Table 10). Thus, the percentage of poorly differentiated SCCs was higher in the arsenism group, while the opposite was true in the non-arsenism group. This finding is consistent with the more aggressive behavior of arsenical SCCs than UV-induced SCCs.

Chronic arsenical exposure is associated with a higher incidence of cancer and mortality from internal organs, especially the lung, urinary tract, liver [10]. It is our routine to perform cancer screen for these malignancies and follow the patients periodically. Although the association of arsenism and internal malignancies is well documented, many clinicians still are not familiar with the characteristic skin lesions of chronic arsenism. As a result, some patients might be treated as isolated cancer cases by various specialists without proper cancer screen and follow-up.

Our study showed that many new arsenical carcinomas continue to develop in the patients with arsenism and many of them unfortunately did not seek for medical help until late stage. This apparently has contributed to a higher age-adjusted cancer morality among the residents in the endemic areas. Our observation underscores the need for integrated programs for cancer diagnosis, treatment and chemoprevention for such patients.

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