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Case Report

Highly Differentiated Plantar Verrucous Carcinoma Secondary to Neuropathy Leprosy Ulcer: Case Report and Literature Review

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Abstract

Malignant transformation of chronic trophic ulcers in leprosy is not rare as it had been considered to be in the past. We described a case of a 77-year-old man diagnosed with lepromatous leprosy (LL) fifty-eight years ago, and skin ulcer initially occurred on the sole of his right foot because of neurovascular dystrophic and had been existing during the last five decades, which had gradually grown into a "cauliflower-like" tumor with mild pain and spontaneous bleeding over last 3 years. No improvement was achieved after oral antibiotic and topical treatment. The patient underwent tumor excision and four toes amputation after the diagnosis of verrucous carcinoma based on lesion histopathologic examination. After 1year follow-up, no metastasis was found.

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Keywords: leprosy; ulcer; squamous cell carcinoma; anesthetic foot

Introduction

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* that is endemic in some developing countries. Incidence of leprosy in China (0.037/100,000) was lower than that in the United States (0.057/100,000) in 2018 [1]. Approximately 30% of leprosy patients developed nerve damage[2]. When the peripheral nerves are affected, sensory, motor and trophic changes can occur in extremities predisposed to ulceration. And chronic trophic ulcers may develop into carcinoma. We herein report a case of highly differentiated verrucous carcinoma secondary to neurovascular dystrophic leprosy ulcer, and the classification, pathogenesis and feature of malignant transformation of chronic leprosy ulcers are also reviewed.

Case Report

A 77-years-old farmer, living in the suburbs of Guangzhou, was admitted to our clinic because of a verrucous lesion for three years on the sole of his right foot on Feb 13, 2019. He was diagnosed with lepromatous leprosy (LL) in 1961, which was cured with dapsone monotherapy in our clinic for 24 months then, except for a non-healing, recurrent ulcer at the same site since 1963. During the last five decades, he had been living in poor hygiene and sanitation condition, while verrucous-like hyperplasia occurred on the surface of the ulcer three years ago, with mild pain and easily induced bleeding. No improvement was achieved by topical antibiotics ointment and disinfection care. Physical examination showed the whole neoplasm of verrucous appearance, more than 10 verrucae-like neoplasms, range from 2 to 7 cm in diameter in the anterior part of the right foot, pusy or hemopoietic discharge was observed between the verrucous bodies when squeezing (Figure 1a), and a round-like solid mass, 5 cm size in diameter on the dorsal of the right foot (Figure 1b). The patient presented concave edema and hyperpigmentation on the lower third of the right leg. No lymphadenopathy was noted. Sensations of pain, touch and temperature were dullness in the right palm. The patient was otherwise healthy.

A skin biopsy was performed on tumor tissue collected from the plantar of the right foot. Histopathologic examination shows hyperkeratosis, parakeratosis and irregular acanthosis. Numerous horn pearls and minimal nuclear atypia were also observed. significant vacuolarization of the squamous epithelium with well-differentiated basal layer, lack of basal mitoses, and the cornea is dispersed in dyskeratosis cell, filled with keratin. Inflammatory cells were mainly lymphocytes, infiltrating around the blood vessels (Figure 2 a-d). A biopsy on the foot tendon and the right inguinal lymph node showed no metastasis. Computerized

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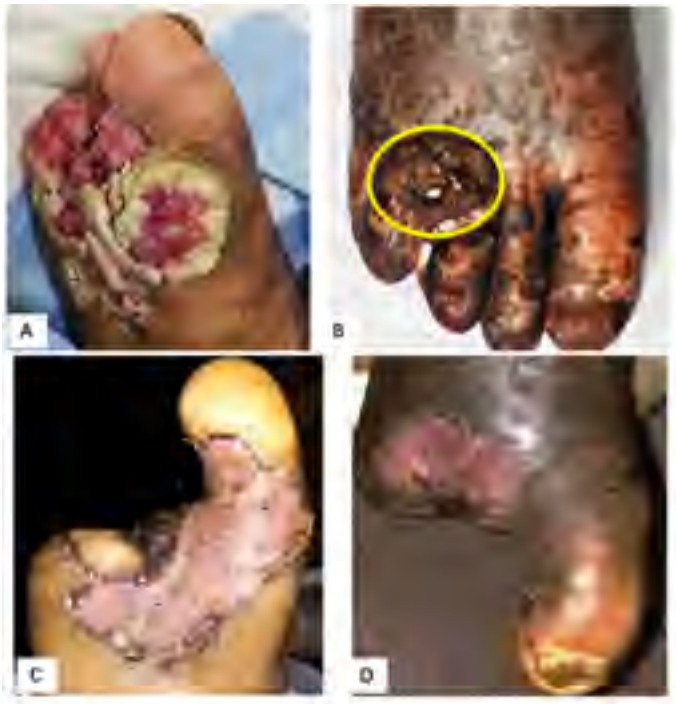

Figure 1. Exophytic verrucous vegetation at the front of right foot. *More than 10 verrucae-like neoplasms, range from 2 to 7 cm in diameter in the anterior part of the right foot, pusy or hemopoietic discharge observed between the verrucous bodies when squeezing (Fig1A) , and a round-like solid mass, 5 cm size in diameter on the dorsal of the right foot (Labelled in yellow highlight, Fig1B,brownness due to bathing of the patient with potassium permanganate). 2 weeks after regional excision surgery with grafting and four toes amputation (Fig 1C palm, Fig 1D back).*

tomography (CT) scan showed that the lesion involved fatty fascia and adjacent muscles, without bone destruction. Colour-Doppler ultrasound revealed arteriosclerosis of bilateral lower extremity arteries.

Based on the clinical and histopathological findings, a diagnosis of verrucous carcinoma (VC) was made. VC is essentially a subtype of SCC, and the VC of the present patient was secondary to a leprous neuropathy ulcer. The patient was performed wide local excision of the lesion with a 1-cm margin with grafting and four toes amputation (Figures 1c and 1d) while no any recurrence was observed after 1 year of follow-up.

Discussion

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae*, affecting peripheral nerves, skin and mucus. If a leprosy diagnosis is delayed or leprosy is not effectively treated timely, the leprosy patients with involvement of peroneal and posterior tibial nerves tend to develop lower extremities or plantar ulcers as a result of irreversible leprosy neuropathy injury. The LL patient de-scribed here was cured with dapsone monotherapy from 1961 to 1963 and left with a none-healing chronic plantar ulcer during 1963-2016. And a verrucous malignancy had been presenting since 2016 until the diagnosis of verrucous carcinoma was made in 2019.

Leprosy ulcer can be divided into two categories, one is skin ulcerated lesions considered as clinical manifestations of an acute phase of leprosy, and this type of ulcer is not a common feature in leprosy patients, except during reactional states, Lucio's phenomenon (LP)[3]. Miyashiro reported that skin ulcers were as part of the main leprosy manifestation in eight patients of multibacillary (MB) leprosy, and the ulcer

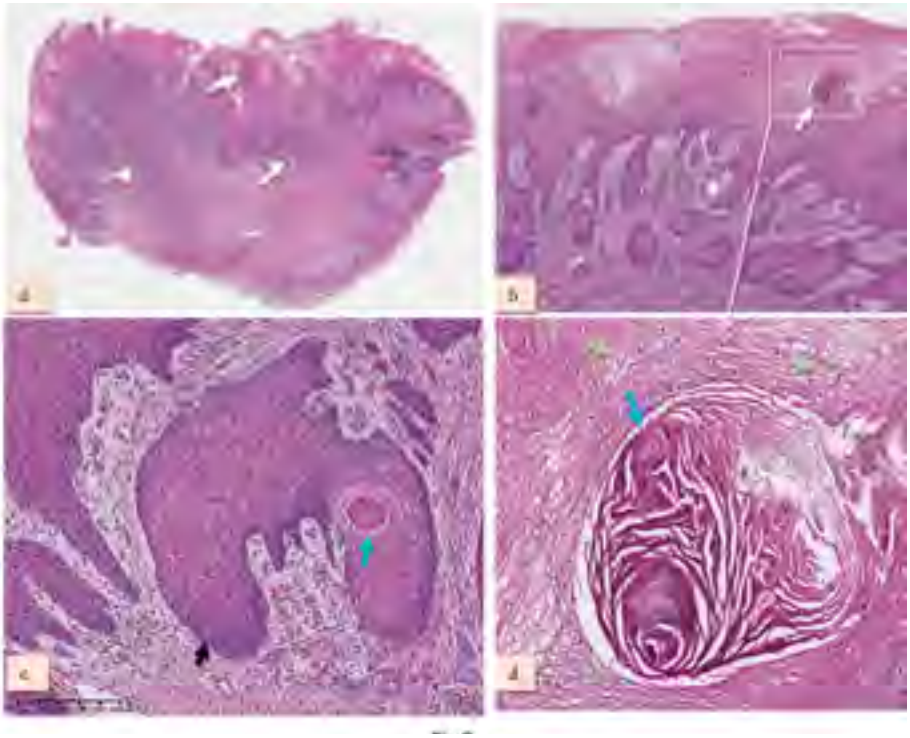

Figure 2. Histopathologic features of tumor tissue (H&E). *Pseudoepithelial-like hyperplasia, intratumoral hyperplasia, hyperkeratosis of the horny layer, and corneal cornea are observed in masses (Fig2a, ×10, and Fig 2b ×100, respectively).and significant vacuolarization of the squamous epithelium (Fig 2d ×200, in green) with well-differentiated basal layer, lack of basal mitoses (Fig 2c ×100, in black), and the cornea is dispersed in dyskeratosis cell, filled with keratin. (Fig. 2c,2d, in blue).*

anatomical sites and rate for the eight patients were lower limb (100%), upper limb (37.5%) and abdominal (12.5%), respectively [3]. The other is chronic trophic ulcer, or neuropathy foot ulceration which is secondary to neuropathies of peroneal and posterior tibial nerves [3]. Chronic neuropathy ulceration is defined as an ulcer occurring at well-defined areas overlying bony prominences in leprosy patient [2,3], which occurs in about 10-20% of patients with leprosy, with the front part of the foot accounting for 71-90% of planter ulcers [2,4,5]. Mustapha et al reported that 76.6% of plantar ulcers were associated with leprosy patients who were released from treatment (RFT) and risk factors including gender, availability and utilization of footwear, age, occupation, and educational status [6]. Ramos et al. [7] reported that chronic trophic ulceration was less frequent in young people in the age group of below 18 years old, perhaps because younger leprosy patients have less time to evolve and to produce neuropathic damage, or a better care enables them to prevent trophic ulceration.

Miyashiro et al. [3] reported non-healing chronic trophic ulceration (e.g. neuropathy ulcers) was the most prevalent ulcer in leprosy patients because of neurovascular dystrophic. There are some dif-ferences between acute leprosy ulcers and neuropathy ulcers secondary to leprosy. First, different from neuropathy ulcers, acute leprosy ulcer is usually positive of anti-acid staining for detection of *Mycobacterium leprae* in target skin specimens. Secondary, acute leprosy ulcer occurs rapidly before treatment and heals rapidly after anti-leprosy treatment. Finally, acute leprosy ulcer is accompanying dramatically inflammation because of immune response to Mycobacterium leprae antigen and immune complexes, whereas neuropathy ulcers result from leprosy nerve injury, and a vascular ischemic malnutritive ulcer, often associated with atrophy, and a less severe inflammation, and occur commonly in plantar areas [3], the neuropathy ulcers does not heal for a long time, and so does malignant transformation [3], e.g. verrucous carcinoma or squamous cell carcinoma occurs(SCC) [4,8,9].

VC caused by chronic ulcer malignancy in leprosy needs to be differentiated from classic SCC. VC is an uncommon well-differentiated, locally invasive, low-grade malignancy SCC. It is also called epithelioma corniculate, cutis papillomatosis carcinoid of gottron, morphologically warty or verrucous, its relatively bland histologic features are often more suggestive of a verruca vulgaris or pseudoepitheliomatous hyperplasia [10], the oral cavity, foot plantar and anogenital region were the three major involvement anatomical sites [8], and it is usually prone to deep penetrating growth, forming many deep crypts filled with keratin and pus, such as a rabbit cavity, pyogenic discharge after extruding the tumor body. Histopathological, the upper part of the lesion resembles ordinary warts, with well-differentiated keratinocytes, and deep invasion of tumor cells, with large stalks that are frequently filled with keratin cysts [11]. Classic SCC is clinically divided into two types, the cauliflower-like (extrinsic) type and the deep infiltrative (endogenous) type. The lesions are hard, solid tumors, with no rabbit cavity-like crypts, and no pyogenic discharge after squeezing, and the tumor edges were elevated and extended encircling, with rapid growth. the clinical presentation of classic SCC varies, ranging from innocuous-appearing lesions to overtly exophytic growth [12]. The first report of malignant transformation of neuropathy ulcers in patients with leprosy was described in 1942, and patients with borderline tuberculoid leprosy (BT) are most commonly affected [13]. Most of SCC were histopathological with a higher grade of differentiation corresponding to Grades I and II and less to grade III and IV of a lower grade of differentiation according to the Broders`s classification [11,14]. More than 70% of leprosy ulcerate associated SCC were histopathologic well-differentiated, followed by poorly differentiated and moderately differentiated SCC [15]. Karthikoyan [16] conducted a study in which 79 Indian patients with leprosy neuropathy foot ulcers were included, foot neuropathy ulcers of the patients were screened for change to malignancy, and 11 cases with the mean age of 60.6 years old with plantar neuropathy ulcers and malignant change were diagnosed during the study period, 10 of 11 were well-differentiated SCC and one VC, Melanoma and basal cell carcinoma (BCC) were rarely observed with only a few cases reported [17,18]. Kampirapap [4] summarized 416 biopsy specimens of chronic ulcers occurring on the extremity of leprosy patients, and results showed that 52.2% specimens were diagnosed histopathological as pseudoepitheliomatous hyperplasia (PH), and 24.5% was reported as SCC, and most of the SCC were localized on the lower extremity, and the sole was the commonest site of involvement

The mechanism of malignant degeneration of chronic neuropathy ulcers in leprosy is not well understood. Several hypotheses were believed in promoting malignant degeneration of chronic neu-ropathy leprosy ulcer, including the overexpression of proto-oncogenes (c-fos and Ha-ras) [19] by chronic inflammation, initiate malignant transformation through growth factor secretion, overexpres-sion of p53 and p21WAF/CIP1 [20]. In addition, high immune cell levels in the ulcerate skin, activated beta-catenin and c-myc in the epidermis may serve as molecular markers of impaired healing[21], and many predisposing factors have been reported, such as ulcers of long duration, constant irritation and traumatization, chronic infection with or without osteomyelitis, poor hygiene, environmental and ge-netic factors, and repeated cytodestructive treatments, such as cryotherapy may contribute to chronic ulcer malignant transformation [13]. Factors implicated in the pathogenesis of VC include constant trauma and irritation and chronic infection [8,10]. The role of human papilloma virus has also been de-scribed, although it is controversial [10] . Richardus et al investigated risk factors for SCC secondary to plantar neuropathy ulcers of leprosy patients, and found that shorter duration of the ulcer and higher use of pesticides may contribute to chronic leprosy ulcer malignant change [22]. In other hand, SCC was known to occur in ulcers of considerable duration. Kampirapap [4] et al studied 416 biopsy specimens collected from chronic leprosy ulcers patients, and 24.5% of them were identified as SCC. Richardus et al [5] summarized 38 consecutive leprosy cases with SCC in chronic ulcer in a review, which showed the average age was 60 years old, the average duration of leprosy was 34 years and the average duration of ulcers was 12 years. Venkatswami et al [9] described a 35-year-old man with a benign trophic ulcer and scarring, because leprosy progressed rapidly to SCC within 12 months. the patient started developing huge inguinal lymph nodes and the ulcer rapidly increased in size, rapid lymphatic spread is unusual in Marjolin's ulcer. Verrucous carcinoma secondary to chronic neuropathy ulceration described here may due to chronic irritation, infection, poor hygiene and sensory loss over the skin area where the damaged nerve involves.

SCC developing from chronic skin lesions has a worse prognosis and higher incidence of me-tastasis than carcinomas arising in previously normal skin, the anatomical site seems to be associated with the metastatic potential of tumor, lesions on the lower limbs present a higher risk than those at other sites [23]. For malignant transformation of chronic ulcers, completely surgery excision remains a choice for treatment. Spyropoulou et al reviewed 24 cutaneous squamous carcinoma who received initial incompletely excision and experienced re-excision and found that incompletely excised lesions may change into a poorer degree of differentiation in re-excision histology reports [14]. The treatment was decided considering the degree of differentiation. For well-differentiated and localized SCC, simple surgical excision with grafting is preferred, and amputation should be considered in the most extensive cases or well-differentiated tumor that are large and/or invasive [24]. Prognostic factors predicting tumor recurrence are size, rate of growth (invasive or non-invasive), and degree of histologic differentiation. In patients with leprosy, well differentiated SCC in chronic ulcers is the most common tumor, followed by poorly differentiated and moderately differentiated SCC which are more likely to spread rapidly to the lymph nodes [13,25].

In a word, after recommending multi-drug therapy (MDT) to leprosy patients by WHO since 1980s, the incidence of chronic leprosy ulcers has been decreasing dramatically. target of the Global leprosy Strategy 2016–2020 was <1 per million cases of G2D amongst newly diagnosed leprosy cas-es[1], and this target was also achieved by China, as the rate of G2D was 0.07 per million cases in 2019. However, the National Programme target of less than 20% of newly detected cases with grade two disability (G2D) by 2020 had not been achieved by the end of 2019; the proportion of G2D in newly detected cases in China in 2019 was 21.6%, China had eliminated leprosy at a national level in 1981 and at a provincial level in 19925; thus, the elimination of leprosy at a county level might be expected in the near future [1].

Conclusion

We concluded from the patient that skin biopsies should be performed on non-healing ulcers. Early diagnosis and resection as soon as possible are the first choice for treatment in highly differentiated VC.

Key messages

1. *A 77-year-old patient of lepromatous leprosy patient with a non-healing ulcer on his right foot after dapsone therapy was diagnosed with verrucous carcinoma and underwent regional excision with grafting and four toes amputation without recurrence.*
2. *Verrucous carcinoma is essentially a subtype of SCC, histopathologic, it is a well-differentiated, locally invasive, low-grade malignancy, and usually prone to deep penetrating growth, forming many deep crypts filled with keratin. It is an uncommon pseudoepithelial-like hyperplasia, clinically mani-festated as verrucous appearance and pusy, pyogenic discharge after extruding the tumor body.*
3. *Neuropathic ulcer secondary to leprosy tends to be malignant, and it is necessary for early diagnosis of ulcer malignancy in none healing chronic foot plantar ulcers.*

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the pa-tient has given his consent for his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be conceal identity, but anonymity cannot be guaranteed.

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Competing of interest

There are no conflicts of interest.

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