CASE STUDY

Early Onset of Squamous Cell Carcinoma Arising From Tuberculosis Verrucosa Cutis

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Abstract A 72-year-old man presented with a chronic scaly verrucous plaque over his right knee for nine months. The lesion was preceded by a well healed scar sustained five years back from a road traffic accident. He was given multiple courses of systemic antibiotic and antifungal medications but to no avail. A skin biopsy confirmed cutaneous tuberculosis. The area of plaque subsided significantly with antituberculosis treatment. However, during the second month of treatment, a new onset of a red fleshy granulating growth developed on the pre-existing site. A repeat skin biopsy revealed squamous cell carcinoma (SCC). He was subsequently referred for surgical excision.

This is presumably the first reported case of SCC arising from tuberculosis verrucosa cutis. While most malignant transformations from tuberculosis has been thought to develop after a long period of time (usually more than twenty-five years), this case report showed that it may also occur within a short period of time. Awareness on this condition is important because any delay in diagnosis and treatment may have detrimental consequences.

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Introduction

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis comprising less than 1% of all tuberculosis.¹ Studies have shown that the Bacillus Calmette–Guérin (BCG) vaccine may not effectively prevent cutaneous tuberculosis.^{2,3} Furthermore, advances in travelling modes

and a significant increase in labour immigration may also lead to an increased incidence of tuberculosis in the future. As an infectious but treatable disease, a high level of awareness regarding cutaneous tuberculosis is important among the medical fraternity.

Case report

A 72-year-old man with underlying diabetes, hypertension and dyslipidemia presented with a chronic crusted lesion over his right knee for nine months (Fig. 1) prior to referral to our clinic. The lesion was preceded by a well healed scar from an abrasion wound

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Fig. 1 Well demarcated thick hyperkeratotic scaly verrucous plaque with a brownish red base and areas of fissuring over the right knee.

sustained five years back from a road traffic accident. The lesion had progressively enlarged over time with crack fissures and purulent discharge. He was given multiple courses of systemic antibiotic and antifungal medications but to no avail.

Physical examination revealed a 9×20 cm irregularly shaped and well demarcated thick hyperkeratotic crusted plaque with a brownish red base and areas of fissuring over the right knee. Diascopy test was negative for apple jelly nodule.

A skin biopsy revealed non-caseating epithelioid granuloma within the dermis with ulceration over the epidermis. Ziehl-Neelsen stain was positive for acid-fast bacilli (AFB). No multinucleated giant cells or malignant cells were seen. Periodic acid-Schiff stain were negative for fungal bodies. Skin biopsy for *Mycobacterium tuberculosis* culture and sensitivity (MTB C&S), tuberculosis polymerase chain reaction (PCR), fungal C&S and fungal PCR were all negative.

The patient had no respiratory symptoms such as coughing, hemoptysis, fever, night sweat, loss of weight or loss of appetite. He was BCG vaccinated and there was no previous contact with tuberculosis patients in the past. Chest radiography was normal, sputum AFB, sputum

MTB C&S were all negative. He was diagnosed as tuberculosis verrucosa cutis (TBVC), and was started on six months of anti-tuberculosis treatment according to WHO guidelines.

Upon completion of two months (intensive phase) of anti-tuberculosis treatment, the size and thickness of the plaque reduced significantly and healed with atrophic scarring (Fig. 2A). However, a new 1.5×2.0 cm well demarcated fleshy red granulating growth developed at the center of the preexisting plaque that seemed to grow larger (2.5×2.5 cm) at three-months of treatment (Fig. 2B).

A repeat skin biopsy revealed a well differentiated squamous cell carcinoma (SCC) (Fig. 3) and the tuberculosis PCR was positive. Computed tomography scan did not show any regional spread or distal metastasis. He was subsequently treated as TBVC complicated with SCC and was referred for a wide local excision of the SCC. A total of six months of anti-tuberculosis treatment was given to this patient.

Discussion

Diagnosis of cutaneous tuberculosis is challenging and highly dependent on clinical correlation. All diagnostic tests for cutaneous tuberculosis have a much lower sensitivity and specificity compared to pulmonary tuberculosis (PTB). It is common to get a negative Ziehl-Nielsen stain, tuberculosis PCR and MTB C&S because of its low sensitivity.^{4,5}

TBVC is a form of cutaneous tuberculosis common in Asia,^{6,7} usually involving the upper and lower extremities. It is usually caused by exogenous inoculation of *M. tuberculosis* into the skin, e.g. after a local traumatic skin injury.⁸ It is the most common form of exogenous tuberculosis which occur in previously sensitized person.⁹ Clinically, our patient suffered from TBVC. The exact path in which TBVC develops can be difficult to assess. Primary inoculation from a traumatic skin injury was the most likely cause in our case.

The diagnosis of TBVC in this patient is based on typical clinical presentation (single scaly verrucous plaque at knee), absence of apple jelly nodules under diascopy, direct AFB visualization histologically, good antituberculosis treatment response and a positive tuberculosis PCR on re-biopsy sample.

Chronic inflammatory conditions such as long standing tuberculosis infection¹⁰ and non-healing ulcer is known to cause malignant transformation. Cutaneous tuberculosis, mainly lupus vulgaris has been reported to be associated with formation of SCC,^{9,10} and in some cases, basal cell carcinoma.¹¹ Possible factors that facilitate carcinogenesis include chronic inflammation,

Fig. 2 New onset of red fleshy well demarcated granulating tissue at the center of the healing TBVC plaque which rapidly grew in size and thickness. (A) at 2 months of anti-tuberculosis treatment and (B) at 3 months of antituberculous treatment respectively.

physical and chemical trauma, cicatricial changes, radiotherapy and sunlight. To the best of our knowledge, this is the first report of squamous cell carcinoma transformation arising from TBVC.

The interval from the onset of cutaneous tuberculosis to the occurrence of carcinoma is usually more than 25 years of untreated disease⁹ while the mean of Marjolin's ulcer takes 30–35 years.¹² There are only a few reports on “acute” malignant transformation of tuberculosis being reported in literature.^{13,14} This particular case report highlights the point that malignant transformation may occur

as early as nine months, a warning sign to the medical fraternity in tuberculosis endemic areas.

Tuberculosis and SCC may mask and mimic each other or coexist concomitantly. Clinicians need to be aware of the various manifestations of both conditions and avoid premature diagnostic closure as misdiagnosis may be detrimental. Commencement of chemotherapy in an SCC patient with co-existent tuberculous infection may lead to immunosuppression and dissemination resulting in fatal infection. On the other hand, a delay in malignancy detection and treatment may lead to a regional spread and metastasis.

Fig. 3 (A) Well differentiated malignant squamous cells arranged in nests with keratin pearls surrounded by desmoplastic stromal reaction. (Hematoxylin and Eosin stain; x 40). (B) The malignant cells were immunoreactive to CK5/6 (x100).

Conclusion

We hope that the sharing of this case may aid similar encounters in future, especially in tropical countries where *M. tuberculosis* abounds. Clinicians should be alert to the possibility of cutaneous tuberculosis with malignant changes if treatment response deviates from its expected course. A high index of suspicion is of utmost importance to prevent complications arising from delayed treatment.

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References

1. Bravo FG, Gotuzzo E: Cutaneous tuberculosis. *Clin Dermatol*. 2007; 25(2):173–180.
2. Akkoc G, Kepenekli Kadayifci E, Karaaslan A, et al: Cutaneous tuberculosis occurring after a skin cut in a child. *Wounds*. 2016;28(8): E31–E34.
3. Ramesh V, Misra RS, Beena KR, Mukherjee A: A study of cutaneous tuberculosis in children. *Pediatr Dermatol*. 1999;16(4):264–269.
4. Tan SH, Tan BH, Goh CL, et al: Detection of *Mycobacterium tuberculosis* DNA using polymerase chain reaction in cutaneous tuberculosis and tuberculids. *Int J Dermatol*. 1999;38(2):122–127.
5. Senturk N, Sahin S, Kocagoz T: Polymerase chain reaction in cutaneous tuberculosis: is it a reliable diagnostic method in paraffin-embedded tissues? *Int J Dermatol*. 2002;41(12):863–866.
6. Aliagaoglu C, Atasoy M, Güleç AI, Özdemir Ş, Erdem T, Engin Rİ: Tuberculosis verrucosa cutis. *Eur J Gen Med*. 2009;6(4):268–273.
7. Pereira MB, Gomes MK, Pereira F: Tuberculosis verrucosa cutis associated with tuberculous lymphadenitis. *Int J Dermatol*. 2000;39(11):856–858.
8. Sharma S, Sehgal VN, Bhattacharya SN, Mahajan G, Gupta R: Clinicopathologic spectrum of cutaneous tuberculosis: a retrospective analysis of 165 Indians. *Am J Dermatopathol*. 2015;37(6):444–450.
9. Santos JB, Figueiredo AR, Ferraz CE, Oliveira MH, Silva PG, Medeiros VLS: Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects – Part I. *An Bras Dermatol*. 2014;89(2): 219–228.
10. Falagas ME, Kouranos VD, Athanassa Z, Kopterides P: Tuberculosis and malignancy. *QJM: Int J Med*. 2010;103(7):461–487.
11. Handog EB, Gabriel TG, Pineda RTV: Management of cutaneous tuberculosis. *Dermatol Ther*. 2008;21(3):154–161.
12. Pekarek B, Buck S, Osher L: A comprehensive review on Marjolin's ulcers: diagnosis and treatment. *J Am Col Certif Wound Spec*. 2011; 3(3):60–64.
13. Ljubenovic MS, Ljubenovic DB, Binic II, Jankovic AS, Jancic SA: Cutaneous tuberculosis and squamous-cell carcinoma. *An Bras Dermatol*. 2011;86(3):541–544.
14. Hagiwara K, Uezato H, Miyazato H, Nonaka S: Squamous cell carcinoma arising from lupus vulgaris on an old burn scar: diagnosis by polymerase chain reaction. *J Dermatol*. 1996;23(12):883–889.