Cutaneous Squamous Cell Carcinoma in Lupus Vulgaris Caused by Drug Resistant *Mycobacterium Tuberculosis*

Abstract

Tuberculosis (TB) is still a major public health problem in the world, with many factors contributing to this burden, including poor living conditions, overcrowding, poverty, malnutrition, illiteracy, and rapid spread of human immunodeficiency virus infection. Cutaneous tuberculosis is a less common form of extrapulmonary tuberculosis, and in this paucibacillary form the diagnosis depends on histopathology, tuberculin positivity, and response to treatment. The diagnosis is even more difficult in cases with drug resistant *Mycobacterium tuberculosis* due to lack of awareness and lack of facilities to diagnose drug resistant tuberculosis. In this article, we describe an unusual case of multidrug resistant lupus vulgaris (LV), in a 34-year-old male who responded to anti-tubercular treatment (ATT) initially, but developed recurrent disease which failed to respond to standard four-drug ATT; subsequently, tissue culture showed growth of multidrug resistant *M. tuberculosis*. Subsequently, he also developed cutaneous squamous cell carcinoma. This article aims to exemplify a grave complication that can occur in long-standing case of LV, the limitations faced by clinicians in developing countries where tuberculosis is endemic, and classical methods of proving drug resistance are generally unavailable or fail.

Keywords: *Cutaneous squamous cell carcinoma, cutaneous tuberculosis, multidrug resistance*

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Introduction

India has the highest burden of tuberculosis (TB). The World Health Organization (WHO) statistics for 2014 gave an estimated incidence of 2.2 million cases of TB in India out of a global incidence of 9 million; the proportion of multidrug resistant TB (MDR-TB) in new TB cases was ~3% and in previously treated cases was approximately 12%.[1]

Cutaneous tuberculosis (CTB) is the paucibacillary form of extrapulmonary TB. Because of the difficulty in isolation of *Mycobacterium tuberculosis* from skin samples and demonstration of acid-fast bacilli (AFB) in histopathology, the diagnosis of CTB rests upon the clinical picture, a positive tuberculin test, and histopathologic features of granulomatous dermatitis supplemented by response to anti-tubercular therapy (ATT).[2-4] Often this simple algorithm is helpful, but of late, the rare occurrence of infections caused by drug resistant tubercle bacilli has complicated the situation leading to uncertainty regarding diagnosis and management of CTB.

Here, we discuss an unusual case of multidrug resistant lupus vulgaris (LV) that subsequently developed cutaneous squamous cell carcinoma (SCC).

Case Report

A male in his forties was referred to us for evaluation of a sudden increase in size of a 16-year-old plaque along the beard area of the face. The lesion initially started as an asymptomatic plaque over the right preauricular area and gradually increased in size. The patient had received multiple treatments with different diagnoses for 5–6 years until a biopsy was done which revealed a diagnosis of LV, for which he was started on four-drug ATT (rifampicin, isoniazid, ethambutol, and pyrizinamide). Within 2 months, he noticed marked improvement and discontinued treatment. Four years later, the lesion recurred and he was restarted on directly observed therapy (DOTS) for 6 months. The lesion improved with treatment but he had extensive hypertrophic scarring, for which he received intralesional triamcinolone injections. After 2 years, he noticed worsening and extension

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of the lesions to the other side. He was restarted on DOTS after biopsy, which was consistent with LV. However, this time he did not show any improvement and the lesions progressed despite ATT. Hence, he was referred to us for further evaluation and management. His general health was otherwise unaffected during this period. He had no history of immunosupression (human immunodeficiency virus infection, diabetes, immunosuppressive medications) predisposing him to extrapulmonary TB or contact with tuberculosis cases and had received Bacillus Camillé–Guérin vaccination as a child. Clinical examination revealed a large 15 × 20 cm exuberant plaque along the beard area of the face with scarring and a large noduloulcerative lesion on the right parotid area with seropurulent and bloody discharge [Figure 1a and b]. Matted lymph nodes were present in the submandibular and submental area.

Histological examination was done from two sites. Biopsy from the margin revealed pseudoepitheliomatous hyperplasia with neutophilic infiltrate and plasma cell infiltration but no granulomas or AFB in dermis [Figure 2]. Tissue biopsy specimens were cultured on BACTEC MGIT 960 System (Becton Dickinson) and showed positive growth for *M. tuberculosis*, which was identified by colony morphology, Ziehl-Neelsen staining, and the conventional biochemical tests as per the standard protocol. Drug sensitivity testing showed that the isolate was resistant to rifampicin and isoniazid. Biopsy from the noduloulcerative lesion revealed islands of well-differentiated keratinizing squamous epithelium with pleomorphism, cytological atypia, and mitotic figures suggestive of a well-differentiated cutaneous SCC [Figure 3]. Patient was started on daily intramuscular injections of amikacin 750 mg and oral ethionamide 250 mg b.i.d., levofloxacin 750 mg b.i.d., clarithromycin 500 mg, and pyrizinamide 1500 mg.

He was referred to the surgical oncology department where a radical excision of the lesion including earlobe, parotid gland, and a functional neck dissection were performed [Figure 4]. The excised specimen showed well-differentiated SCC with free margins. Lymph nodes showed a granulomatous pathology. A final diagnosis of well-differentiated SCC, T4 N0 M0, arising from LV was made. Patient was continued on modified ATT for 18 months. and followed up for 1 year, during which he did not develop any relapse of TB or carcinoma.

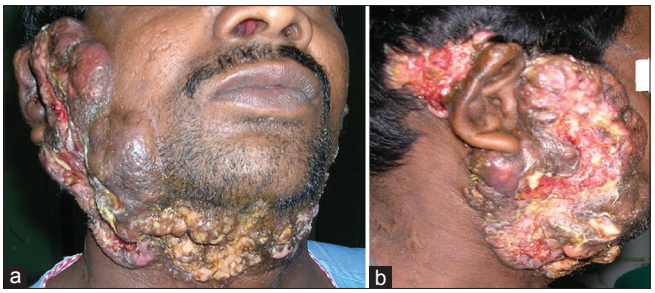

Figure 1: (a, b) Exuberant verrucous skin-colored tumorous plaque along the beard area of the face

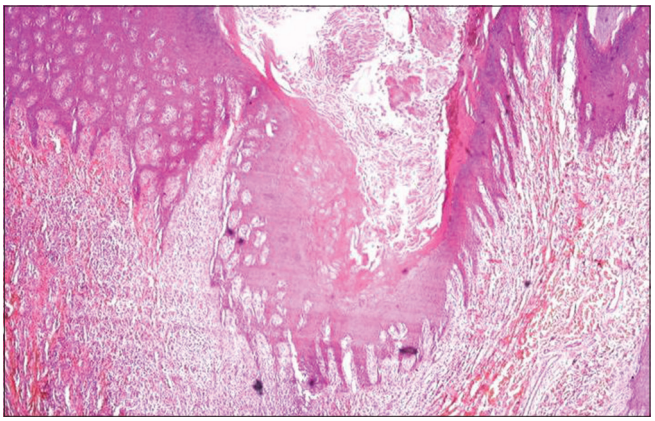

Figure 2: Skin biopsy from the lesion showing a pseudoepitheliomatous hyperplasia, dermis showed neutophilic infiltrate along with plasma cell infiltration, suggestive of chronic infection (H and E, ×40)

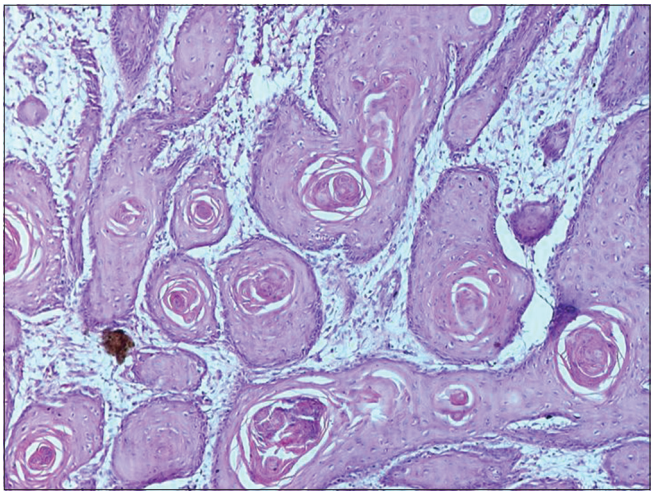

Figure 3: Histopathology showing islands of well-differentiated keratinizing squamous epithelium with pleomorphism and mitotic figures, suggestive of a well-differentiated squamous cell carcinoma (H and E, ×40)

Discussion

CTB is a relatively uncommon form of TB, comprising approximately 8.4–13.7% of all tuberculosis and 1.5% of all extrapulmonary TB manifestations.[5]

The diagnosis of CTB is not an easy task as low bacillary load makes isolation of organisms difficult on culture and histopathology. Diagnosis of drug resistant TB is even more difficult as molecular tests for detection of resistance have low sensitivity.[6,7] The exact incidence of drug resistance in CTB is not known because there are only isolated case reports and small series of drug resistant CTB.[8-10] The lack of awareness about drug resistant CTB and probably a lack of facilities for diagnosis was probably the reason why our patient was diagnosed late and prescribed ATT 2–3 times.

Another important concern in our patient was the development of SCC. The incidence of SCC arising from LV ranges from 0.5% to 10.5% with an average of 4%.

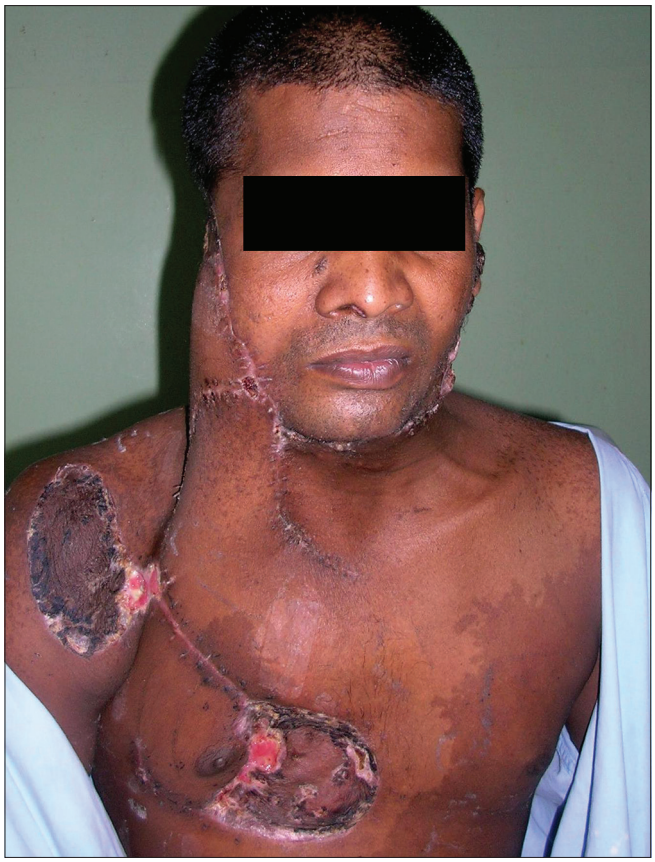

Figure 4: Posttreatment photograph of the patient

The interval from the onset of LV to SCC ranges from 2 to 79 years.[11,12] Although the mechanisms of the neoplastic process are not fully explained, Kennsler *et al*.[13] suggested that free radicals originating in chronic inflammation could promote tumor development. SCC in LV scars is localized in a majority of cases on sun-exposed areas of the body suggesting the role of ultraviolet radiation. In many studies, not only DNA-damage but mutations of the p53 gene and immunosuppression produced by ultraviolet light have been implicated in inducing malignancy.[14] In our patient, malignant transformation seems to be the result of chronic (approximately 16 years) inflammation, UV exposure, and local immunosuppressants such as steroids, creating a locus minoris resistentiae. MDR *M. tuberculosis* may be a coincidental finding in this case or it may have contributed indirectly to development of malignancy in this patient by causing a chronic nonhealing lesion that did not respond to treatment.

This article aims to exemplify a grave complication that can occur in long standing case of LV and the limitations faced by clinicians in developing countries where tuberculosis is endemic and classical methods of proving drug resistance are generally unavailable or fail. It has been advocated that, in pulmonary TB, drug resistance patterns in any given setting should be taken into account, and in order to curtail the spread of infection in the community, second-line drugs should be started judiciously in those who have failed to respond to first-line ATT when there is a strong suspicion of MDR-TB infection and while the sensitivity report is awaited. However, the same criterion cannot be extended to CTB in which culture is often negative. MDR CTB may not be fatal but causes significant morbidity, hence, we need to develop guidelines for management of such cases, taking into account the tolerability, toxicity, duration of treatment, and expected outcomes of treating such infections. This case report underscores the need to develop tests for the early diagnosis of MDR-TB because failure to effectively deal with it could prove disastrous for both the patients and community.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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