Cutaneous lupus vulgaris: Bringing the wolf out of the darkness
Mary Thomas* and Meryl Antony  

1Fellow in Dermatosurgery, Department of Dermatology, St. John’s Medical College and Hospital, Bangalore, Karnataka, India
2Assistant Professor, Department of Dermatology, St. John’s Medical College and Hospital, Bangalore, Karnataka, India

Abstract
Lupus vulgaris is the commonest form of cutaneous tuberculosis accounting for about 75% of the cases. Clinical dermatologists need to be aware of the myriad clinical presentations of this condition as it can be misdiagnosed especially when the index of suspicion is low. It is important to make a diagnosis and promptly treat as it can be disfiguring and destructive.

Introduction
Tuberculosis (TB) is one of the oldest known diseases with evidence of the disease being found in the vertebrae of the Neolithic man in Europe and in Egyptian mummies. It was not until 1882 that Robert Koch discovered the causative agent Mycobacterium tuberculosis [1]. Though improved living standards, the BCG vaccine and standardised chemotherapy have greatly reduced the disease burden of tuberculosis, in the current era of HIV, co-infection with tuberculosis (incidence 17.4%) is still a major concern especially in developing countries [2].

Lupus vulgaris (LV) is the commonest form of cutaneous TB accounting for 75% of the cases. It was first described by Erasmus Wilson in 1865 who compared the clinical appearance of the lesions to the ravages of a wolf [3,4]. Various clinical forms of the disease have been reported, many of which are close mimics of other common dermatoses in the tropics [5]. This, and its association with systemic TB make it essential to have a clear understanding of LV.

Epidemiology
LV, also referred to as “tuberculosis luposa” and “tuberculosis luposa cutis” is more common in males with a male to female ratio of 6.8:1 [6,7]. The disease generally begins before puberty, and has been reported to occur as early as 18 months of age [8]. Due to the asymptomatic nature and slow progression of the lesions, the patients present late. The duration of illness varying between 3 months to 50 years before medical help is sought [9,10]. LV is more common in the tropics among the lower socioeconomic group. The clinical presentation varies with the geographic location. In Europe, over 80% of the lesions occur on the head and neck, particularly on the nose and cheek [11], whereas in the tropics lesions are noticed more commonly on the extremities and buttocks. This difference has been attributed to the increased environmental temperature encountered in the tropics and cultural practises like sitting on the ground and walking bare foot [4].

Causative organisms
Though the commonest causative organism is M. tuberculosis, few reports of lupus vulgaris associated with M. bovis, especially M. bovis spp caprae [12], Bacillus Calmette-Guerin [13,14] and M. xenopi [15] have been reported. The mode of infection is thought to be endogenous or exogenous inoculation following minor trauma including tattooing [16,17] and ear piercing [18]. Multiple reports of the occurrence of LV following BCG vaccination have been documented [13].

Clinical features
LV starts as a soft brownish red papule or nodule that gradually expands by involution in one area with expansion in another, gradually progressing over a period of many years to form a well-defined skin-coloured to erythematous plaque with an “apple jelly nodule” appearance on diascopy [19]. The plaque is characterised by evidence of healing and atrophic scarring in some areas interspersed between areas of activity giving a wolf bitten appearance. The lesions are usually located on the buttocks, thighs and occasionally on the face [20]. Lesions involving the genitalia [21,22], nasal mucosa [23-25] and auricular cartilage are rare but associated with severe disfigurement [4]. Other uncommon sites include the oral mucosa [26], larynx [27] and conjunctiva [28]. Ocular involvement with extension to the globe [29], occurrence at the site of BCG vaccination [14] and in the vicinity of scrofuloderma [30] and lesions in a “necklace distribution” have also been reported [31]. Indurated plaques of LV on the earlobes causing “turkey ears” is a recently described sign of LV [32]. An eczematous variant, “Lupus vulgaris erythematoides “has been described [33]. Though the lesions are mostly unilateral, cases with bilateral earlobe involvement and disseminated lesions have also been reported [34-36].

The commonly encountered clinical variants include classic plaque or keratotic type, hypertrophic, ulcerative, atrophic and planar [37]. Of these, the keratotic type is the most common whereas ulcerative and atrophic forms are the least common [38]. Bhutto et al. [20] described four major types of lupus vulgaris:

Correspondence to: Dr. Mary Thomas, Fellow in Dermatosurgery, Department of Dermatology, St. John’s Medical College and Hospital, Bangalore, Karnataka, India- 560024, Tel: +9199916993757; E-mail: mary_thomas121@yahoo.com

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1. Psoriasiform type: Single or multiple flat plaques varying in size and shape with annular, oval or irregular borders on a non erythematous base. The lesions are covered with thick silvery scales resembling psoriasis. Lesions commonly occur on the legs, knees and back (Figure 1).

2. Nodular type: Multiple nodules with the classically described “apple jelly” appearance surrounding a single larger plaque with a clear or sometimes atrophic centre. These lesions are frequently located on the thighs and hips (Figure 2).

3. Papular type: Small reddish-brown to skin-coloured papules. The lesions closely resemble cutaneous leishmaniasis and are seen mostly on the cheek and rarely on the nose and abdomen.

4. Erythematous type: Erythematous plaques of 2-5 cm with irregular margins with minimal scaling on the surface, clinically resembling eczema. The affected sites include the face, hips and arms (Figure 3).

Other unusual presentations include sporotrichoid lesions [39], annular lesions [40-42], disseminated lesions [34-36], giant lesions [37] (Figure 4) and lesions mimicking granulomatous folliculitis [43].

Although regional lymphadenopathy is not uncommon [44], in rare cases when the lymph nodes have been destroyed due to intense tissue reaction, the patients develop lymphedema. LV associated with esthiomene has been documented [45].
The association of LV with systemic TB is seen in 10-30% cases [38]. Concomitant active TB elsewhere involving the lungs, bones, liver and other organs can be demonstrated in only 10% to 30% of the cases, and approximately only one half of the cases have history of past infection [46]. Papulonecrotic tuberculids [36], scrofuloderma [30,47], TBVC [6] and lichen scrofulosorum [48] have been reported to coexist with LV. Miliary TB has been rarely associated with LV and is hypothesised to occur following a drop in the patient’s immune status [44].

Various malignancies have been reported to occur in long standing cases of LV including SCC in 8% cases [49] and BCC [50,51]. One case of LV associated with Non Hodgkin’s Lymphoma has been reported [52].

In the immunocompromised host

Though lupus vulgaris is uncommon in the immunocompromised host, both solitary and disseminated lesions have been reported. The clinician must be aware that multiple forms of TB can occur concomitantly in such situations and the patient must be investigated and treated accordingly [53].

Differential diagnosis

LV mimics various other tropical dermatoses and can often be misdiagnosed clinically as TBVC, leishmaniasis, Hansen’s disease, syphilis and deep fungal infections e.g. Madura mycosis, sporotrichosis and chromomycosis [20,38,39]. Lesions on the face may be mistaken for DLE in view of the atrophic scarring [4]. Early lesions resemble a Spitz nevus or a haemangiom [54]. Other common dermatoses that need to be excluded are psoriasis [55-57], eczema [33], sarcoidosis, pseudolymphomas [58], hypertrophic lichen planus, lichen simplex chronicus [59], tinea corporis [41] and blastomycosis [60]. Lesions may mimic squamous cell carcinoma and lead to a diagnostic dilemma especially in long standing lesions as SCC is known to develop in 1-2% of cases over a period of 10-30 years [61].

Lesions on the nasal mucosa may mimic other granulomatous lesions including lepromatous leprosy, Wegener’s granulomatosis and syphilis with destruction of the nasal cartilage and deformity [24].

Investigations

The diagnosis of LV requires a full workup including a detailed history and a thorough physical examination. Due to its myriad forms, a high index of suspicion is the key to making the diagnosis. Laboratory investigations should aim at both confirming the diagnosis of lupus vulgaris and excluding other foci of tuberculosis.

In LV the tuberculin test or Mantoux skin test becomes positive 2-10 week s following infection and has a sensitivity between 33% and 96% and specificity of 62.50% with a cut-off of 10 mm. In unvaccinated populations, the sensitivity is close to 97% [62]. Fine needle aspiration cytology, though not commonly used in the diagnosis of LV, shows cohesive epithelioid cell granulomas with or without chronic inflammatory infiltrate in 89%; however, Acid Fast Bacilli (AFB) can be demonstrated only in 22.2% cases [63]. Interferon-γ release assays performed on whole blood, like QuantiFeron-Gold and T-SPOT have been rapidly gaining popularity due to their high specificity and speed even though the sensitivity in cutaneous TB is average [64].

A biopsy is considered the pillar for identification of cutaneous TB [65]. The sample can be utilized for the following tests:

1. Tissue smears
2. Histopathology
3. Bacteriological cultures
4. PCR

Tissue smears do not demonstrate bacilli but help exclude other mimics e.g. leishmaniasis. Cultures have a higher sensitivity (up to 90%) and may detect as few as 10-100 bacilli/ml. However, the delay of 3 to 6 weeks required for culture results currently limits their use in the diagnosis of tuberculosis. Though the Lowenstein- Jensen medium, one of the oldest and only tested media is still in use, newer popular media for the culture of M. Tuberculosis include biphasic (MB-Check; Nippon Roche Co., Ltd., Tokyo, Japan) and radiometric (BACTEC; Nippon Becton Dickinson Co., Ltd., Tokyo, Japan) liquid-based culture systems and egg-based media (3% Ogawa and Ogawa K). Mycobacterial growth is better on an egg-based medium, but quicker on agar medium. Liquid systems allow for rapid growth (1–3 weeks), while growth on solid media can take from 3 to 8 weeks. The BACTEC- MGIT 960 and BACTEC460TB are of the most popular tests.

The MycoDot test, which is a lipoarabinomannan (LAM) antigen ELISA sensitivity and specificity of 26-81% and 92-100% respectively.

Currently, though PCR appears to be the most useful in multibacillary forms of CTB, its utility in the paucibacillary forms like LV is limited [54]. In one report of AFB-negative specimens, the overall sensitivity of PCR was found to be 50 to 72 percent [66]. In a study by Suthar et. al. none of the patients showed a positive reaction on mPCR test. DNA PCR is more useful with a sensitivity of 25% and a specificity of 73.7%. Hence, the results of PCR should be interpreted cautiously in the light of clinical and histological findings [67]. Though the value of genotyping has been established in various other forms of TB especially in this era of drug resistance, it has not been well studied in LV.

Definite laboratory confirmation requires a positive culture of tubercle bacilli but this is not essential for routine clinical diagnosis [64].

Histology

The characteristic histological features of LV are well formed granulomas without caseation AFB are usually absent. The epidermis may be atrophic or hypertrophic, with acanthosis, papillomatosis and pseudop epitheliomatous hyperplasia. The epidermal changes will vary based on the clinical presentation. Well defined tuberculoid granulomas composed of Langhans giant cells and mature epitheloid cells with a dense lymphocytic infiltrate with plasma cells located in the mid dermis is characteristic. Occasionally the granulomas may be sarcoidal or mixed. Caseation is rare and may occur within small foci of the granuloma (Figure 5). AFB are infrequently detected. A deep biopsy is highly recommended to visualise the entirety of the granuloma. Due to the paucibacillary state, the Zeil Nielsen stain has limited utility [54].

Histological differential diagnoses include sarcoidosis, tuberculoid leprosy, deep fungal infection, and foreign body reaction [68].

Treatment

Over the years, various treatment modalities have been tried for LV including mercury [69], potassium iodide [70], arsenic [71] and vitamin D2 [72]. In 1903, Niels Ryberg Finsen was awarded the Nobel Prize for his invention of light therapy for skin tuberculosis (lupus vulgaris). The mechanism of action has been hypothesised to be by the...
production of singlet oxygen through radiation of porphyrins with light leading to destruction of the mycobacteria [73].

Surgical excision and flap reconstruction has been successfully attempted with no recurrence on long term follow up. Though the advantage of this therapeutic approach is that there is quick eradication of the disease avoiding the unsightly wolf bitten scar, it is not a recommended modality of treatment as microscopic spread to the lymph nodes and other sites will not be treated. Recurrences have been reported with such an approach [74].

Earlier reports indicate that lupus vulgaris has been treated with Isoniazid alone [75,76], but this may lead to the emergence of drug resistant strains of M tuberculosis especially if extracutaneous sites are involved this practice should be discouraged.

As controlled trials are lacking for the treatment of cutaneous TB, the recommendations from trials on pulmonary and other extracutaneous forms of TB have been incorporated into the treatment guidelines. Currently, the treatment of all types of tuberculosis is by the directly Observed Treatment Short Course (DOTS) strategy, which is implemented by World Health Organization (WHO) [77]. Most DOTS regimens have thrice-weekly schedules (Monday-Wednesday-Friday). For cutaneous tuberculosis the recommended treatment involves an intensive phase consisting of Rifampicin (R-450 mg), Isoniazid (H-300 mg) Ethambutol (E-1200mg) and Pyrazinamide (Z-1500 mg) administered for three days in a week for 2 months. This is followed by the continuation phase in which R-450 mg and H-600 mg given three days in a week as a continuation phase for 4 months [78]. This strategy has been found to be efficacious with most cases responding well by the end of the intensive phase with no reported relapses [64,78]. Depending on the clinical response, the duration of treatment can be extended. For children and adults who weigh less than 30 kg, these drugs are administered according to their body weight.

Conclusion

Lupus vulgaris is the commonest form of cutaneous TB with diverse clinical manifestations. It is important to make a diagnosis and promptly treat as LV can be disfiguring and destructive.

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