Dermatol Ther (Heidelb) (2015) 5:67–76
DOI 10.1007/s13555-014-0066-x

CASE REPORT

# Lewandowsky's Rosaceiform Eruption: a Form of Cutaneous Tuberculosis Confirmed by PCR in Two Patients

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Received: May 26, 2014 / Published online: December 18, 2014


## ABSTRACT

***Introduction***: Cutaneous tuberculosis (TBC) is a chronic disease caused by *Mycobacterium tuberculosis*, and is present in less than 1–2% of all TBC cases. The current problem with diagnosis is the demonstration of bacillus in the skin, especially paucibacillar forms, where sources like polymerase chain reaction (PCR) have improved diagnostic capacity.

***Case Presentation***: Two cases of cutaneous TBC are reported. The first patient was 52-year-old woman with facial erythematous papulo-nodular lesions which had been developing for 4 months, and had previously been treated as acne rosacea, with partial response. Histopathological studies showed chronic granulomatous inflammation. TBC was suspected, so PCR was performed, which showed positive for *M. tuberculosis*. The second case was a 43-year-old woman with a facial rosaceiform plaque which began 6 months previously, and was treated as rosacea without any change for 5 months. Skin biopsy and PCR were positive for TBC. Both cases were treated using primary schedule for TBC, and both presented a favorable response.

***Discussion***: A clinical profile called Lewandowsky's rosacea-like eruption has been previously described. The condition has been questioned for years and was later removed from the spectrum of tuberculids and cutaneous TBC for not being able to isolate microorganisms in skin samples, a situation that might now change. In paucibacillar forms, when culture and staining are negative and TBC is still suspected, it is recommended to use DNA amplification by PCR for an accurate diagnosis. Both cases bring up the

**Electronic supplementary material** The online version of this article (doi:10.1007/s13555-014-0066-x) contains supplementary material, which is available to authorized users.

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concern about once again bringing Lewandowsky's rosaceiform eruption into the spectrum of cutaneous TBC, and the discussion about the current definition of tuberculid.

**Keywords:** Lewandowsky; Polymerase chain reaction; Tuberculid; Tuberculosis

## INTRODUCTION

Cutaneous tuberculosis (TBC) is a chronic disease caused by *Mycobacterium tuberculosis* and occurs in less than 2% of all cases of extrapulmonary TBC, with an incidence of 0.5–0.6%, and an estimated association between cutaneous and visceral TBC of 28% of all cases [1]. It can appear as a manifestation of a systemic infection, although it can also exist as primary cutaneous TBC [1, 2]. The most frequent forms are scrofuloderma and lupus vulgaris [3, 4]. Clinical manifestations of cutaneous TBC can be classified by their dissemination in endogenous and exogenous infections [5], and according to local bacterial concentrations in multibacillary (high bacillary concentration) and paucibacillary (low bacillary concentration) lesions [4], in which extreme tuberculids are found [6]. Multibacillary forms can be caused by direct inoculation (tuberculous chancre), by continuity (scrofuloderma, periorificial cutaneous tuberculosis), or by hematogenous spread (acute miliary tuberculosis and tuberculous gumma), while the paucibacillary forms of cutaneous TBC can be produced by direct inoculation (tuberculosis verrucosa cutis, lupus vulgaris in some cases, and tuberculids) or by hematogenous dissemination (lupus vulgaris and tuberculids) [5]. In the case of multibacillary forms, cultures and stains like Ziehl–Neelsen usually show positive results for *M. tuberculosis*, confirming diagnosis by this way [2, 4, 6]. However, in paucibacillary forms, due to the low bacillar concentration found locally in lesions, tests for bacillus may be negative. The actual problem of diagnosis in cutaneous TBC is therefore the demonstration of bacillus in skin biopsies, particularly in paucibacillary forms. This has forced use of new diagnostic resources, and polymerase chain reaction (PCR) has improved global diagnostic accuracy [7–9]. In this article, two cases of cutaneous TBC with histopathology of tuberculid and rosaceiform lesions are presented; both cases were diagnosed using PCR. In addition, a brief literature review will discuss reconsidering Lewandowsky's rosaceiform eruption [10, 11] once again into the spectrum of cutaneous TBC.

## CASE PRESENTATION

### Case 1

A 52-year-old Chilean woman presented with facial erythematous papulo-nodular and pruriginous lesions which first occurred 4 months previously in both glabellar regions. These legions extended progressively to the rest of the face, with confluence zones and an association with scratching (Fig. 1). She had no relevant medical history or contact with patients with known TBC, and had been vaccinated with Bacillus Calmette–Guérin (BCG) after birth. She had been previously treated for 3 months for acne rosacea using different drug therapies (oral doxycycline 100 mg every 12 h, followed by oral isotretinoin 20 mg per day, and topical treatment with alpha-bisabolol 1% and metronidazole gel 1%) with partial response. Laboratory examinations [C-reactive protein, C3, C4, anti-neutrophil cytoplasmic antibodies

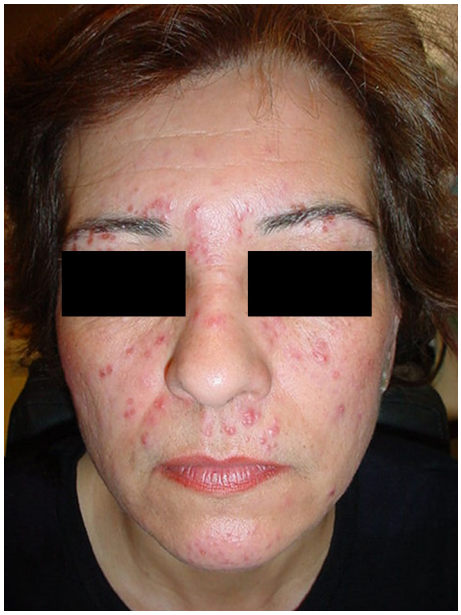

**Fig. 1** Papulo-erythematous lesions, similar to those presented in acne rosacea

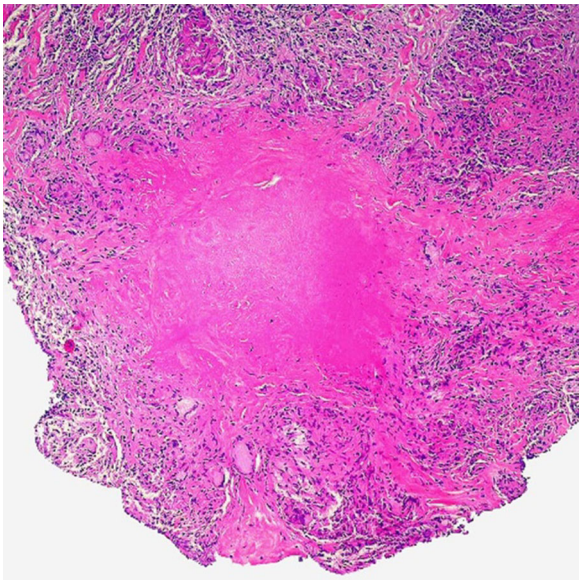

**Fig. 2** Cutaneous biopsy, H–E stain, 100×. Necrotizing granulomatous dermatitis with caseification, and Langerhans cells located in deeper reticular dermis layer

(ANCA), anti-proteinase 3 (anti-PR3), anti-myeloperoxidase (anti-MPO), lupus erythematosus (LE) cells in peripheral blood sample] were either negative or in the normal range, but an antinuclear antibody (ANA) test was positive in 1:640 dilution with NuMA-1 pattern. Lupus erythematosus was suspected, so skin biopsy and direct immunofluorescence assay (IFD) were performed. Histopathological study showed chronic histiocitary and lymphoplasmocitary inflammatory process, with numerous granulomas with central caseificant necrosis and giant multinucleated Langerhans cells (Fig. 2) (cytology and histopathology laboratory, Catholic University Health Network), while IFD was negative for C3, immunoglobulin A (IgA), IgG, IgM and fibrin. Because of these findings, cutaneous TBC was suspected, and so PCR for *M. tuberculosis* was requested. PCR technique was done using amplification in duplicate for sequence IS6110 [specific for Mycobacterium tuberculosis complex (MTC)] [12]. Evaluation of DNA's integrity from the sample was performed by amplification of human beta-globin gene (positive internal control) and a water-only sample ($H_2O$), to discard the possibility of contamination (negative external control) [13] (cytology and histopathology laboratory, Catholic University health network). PCR result was positive for TBC (Fig. 3). Tuberculin test with Mantoux technique [purified protein derivative (PPD)] was requested to determine her sensitivity to the bacillus (injection of 2 tuberculin units per 0.1 mL volume, using PPD RT-23) [14], and resulted in positive erythema and 5 mm of induration 72 h later (assessed at Medical Specialties Center, Carlos Van Buren Hospital, Valparaiso). A chest radiograph (X-ray) and computed tomography (CT) scan of thorax, abdomen and pelvis, urine exams and serum chemistry panel were all negative. Treatment was started with a primary schedule of 6 months (using isoniazid 300 mg + rifampicin 600 mg + pyrazinamide 1,500 mg + ethambutol 1,200 mg daily for the first 2 months; and isoniazid

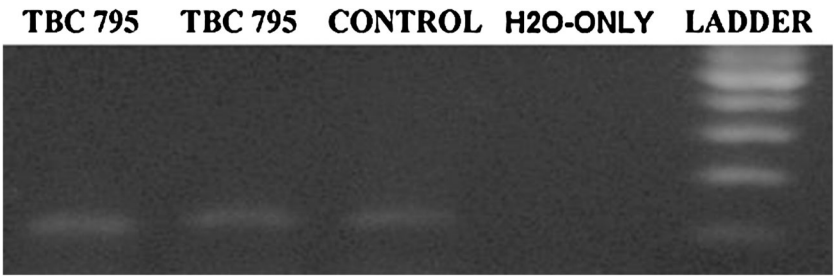


**Fig. 3** Electrophoresis in agarose gel for the products of double amplification of the insertion sequence IS 6110, specific for *Mycobacterium tuberculosis* complex (MTC). *Column 1* DNA extract from cutaneous sample. *Column 2* duplicate of *line 1*. *Column 3* evaluation of the sampling DNA integrity by amplification of the human beta-globin gene (positive internal control), that shows good DNA preservation. *Line 4* water-only sample ($H_2O$) without amplification that discards the possibility of contamination (negative external control). *Column 5* DNA stair of 100 bases pairs, used for measuring the products. Interpretation of the meaning of positive amplification of IS6110, specific for MTC, must always be done in the clinical and histopathological context of the sample sent for analysis

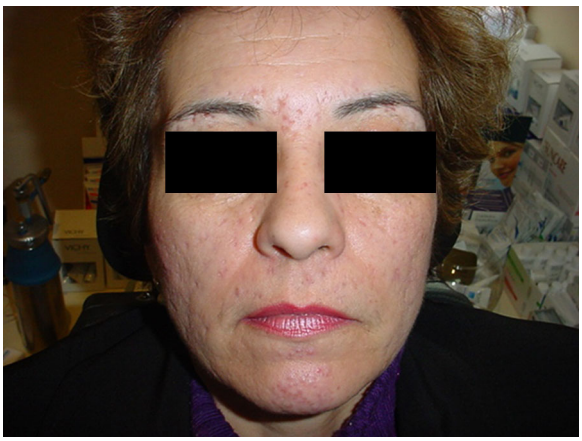

**Fig. 4** Medical control at 6 months of treatment using primary schedule for tuberculosis, with significant improvement and atrophic scars as sequels

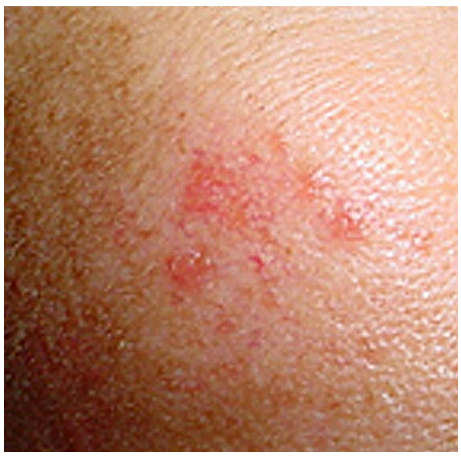

**Fig. 5** Cheek with a rosaceiform plaque, papules and telangiectasies

800 mg + rifampicin 600 mg for the subsequent 4 months). The patient responded positively to treatment, evident after 30 days of treatment, with complete clearance of lesions at the end of the treatment (Fig. 4).

## Case 2

A 43-year-old woman presented with a rosaceiform plaque, which had been developing for 6 months, with papules and telangiectasies, and erythematous base in her right cheek (Fig. 5). There was no relevant medical history, or contact with patients with known TBC, and she had been vaccinated with BCG after birth. Treatment for Rosacea was started, with no changes over 5 months. Because of the persistence of the lesions and the poor therapeutic response, skin biopsy and IFD were indicated. Histopathological tests also showed superficial dermis with marked and diffuse lymphocitary infiltrate, with epithelioid histiocytes and formation of granulomas; results that were compatible with

tuberculids (Fig. 6) (cytology and histopathology laboratory, Catholic University Health Network). IFD was negative for C3, C1q, IgA, IgG, IgM and fibrin. Similarly to Case 1, presence of *M. tuberculosis* was suspected as a diagnostic possibility, and so PCR was requested. The technique used was carried out in duplicate, and was consistent in amplification for the sequences of the heat shock protein 65 Kd (generic for *Mycobacterium*) and IS6110 (specific for MTC) [12]. At the same time, DNA integrity of the skin sample was evaluated by amplification of the human beta-globin gene (positive internal control) and a water-only sample ($H_2O$) to discard the possibility of contamination (negative external control) [13]. Results of the PCR were positive for *M. tuberculosis* (cytology and histopathology laboratory, Catholic University Health Network). Tests for PPD showed negative results, without erythema or induration (Medical Specialties Center, Carlos Van Buren Hospital, Valparaiso). Treatment with primary schedule was started (using the same schedule as Case 1), showing a rapid response after 15 days of treatment (Fig. 7). Tests for the primary focus did not show the presence of TBC.

Informed consent was obtained from all patients for being included in the study.

## DISCUSSION

Prevalence of TBC in Chile has diminished during the last few decades, reaching a rate of 13.3/100,000 in 2006 [15]. However, with the recent outbreak of human immunodeficiency virus (HIV), the use of novel immunosuppressive drug therapies, the emergence of multidrug-resistant TBC strains, and migrations of population, the current context may change [5, 16]. This situation is particularly reflected in HIV and acquired immune deficiency syndrome (AIDS) patients, in whom prevalence of TBC is significantly higher than in the general population [17]. Cases of extrapulmonary TBC are usually more difficult to diagnose [18]. This is particularly relevant in paucibacillary forms of cutaneous TBC, where tests for bacillus may be negative. At

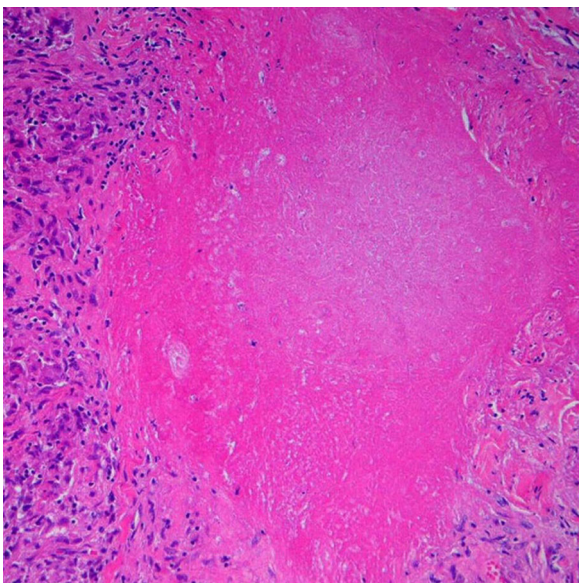

**Fig. 6** Cutaneous biopsy, H–E stain, 200×. Caseificant granuloma with cells arranged in a palisade

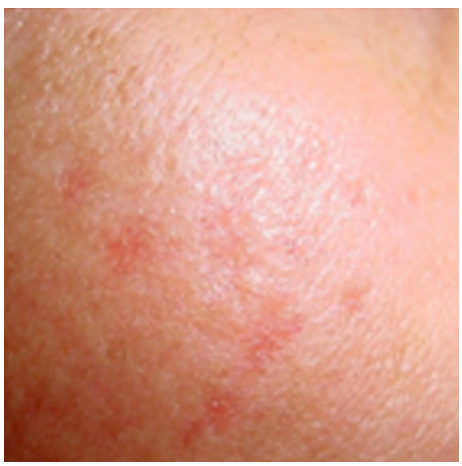

**Fig. 7** Results at 15 days of treatment using primary schedule for tuberculosis

the extreme of the spectrum are located the tuberculids (papulonecrotic tuberculid, Bazin's erythema induratum, and lichen scrofulosorum), considered to be cutaneous hypersensitivity eruptions to *M. tuberculosis* that occur in patients previously exposed with moderate or high levels of immunity against the microorganism. Tuberculids must comply with the following conditions: (1) there must be histopathologic evidence for the presence of granulomatous inflammation in skin lesions; (2) there must be a failure to detect *M. tuberculosis* in Gram stain and cultures of affected tissue; (3) there must be cutaneous lesions that heal with anti-TBC treatment; and (4) there must be a presence of detectable extra-cutaneous *M. tuberculosis* infection (active or latent), a strongly positive tuberculin skin test, or a positive interferon-gamma release assay [6, 19].

The clinical features of cutaneous TBC are diverse and vary from asymptomatic to painful and pruritic lesions as result of exogenous and endogenous spread of *M. tuberculosis* and from immune-mediated mechanisms [20]. More often, cutaneous symptoms have appeared during treatment of pulmonary TBC as tuberculosis-associated adverse drug reactions [21]. In our report, the first patient presented pruriginous lesions. Although rare, pruritus has been described in cases of tuberculids, especially in papulonecrotic tuberculids [22–25]. Immune mechanisms are yet to be understood, but several authors have proposed that tuberculids (erythema induratum of Bazin, papulonecrotic tuberculid) represent delayed-type IV hypersensitivity reactions mediated by antigen-specific effector T cells [26–28]. In this immune reaction, symptoms such as itching are associated with increased production and release of cytokines, neurotrophins and neuropeptides, and are regulated by infiltrating tissue resident cells [29]. Cytokines and chemokines are inflammatory mediators and important activators of sensory nerves, thereby contributing to neurogenic inflammation, pain and pruritus [30]. Recent findings have identified potential classes of endogenous "itch mediators" and established a modern concept for the pathophysiology of pruritus [29, 31].

Due to its low bacillary concentration, it has been discussed whether to define tuberculids as produced by the presence of the bacillus in the skin, or if it is produced by hypersensitivity reactions [11]. Lewandowsky described in 1917 a clinical form that he called Lewandowsky's rosaceiform tuberculid [10], considered initially inside the spectrum of tuberculids [32–35]; however, this was later criticized by authors like Snapp et al. [11], because of the impossibility to isolate microorganisms in skin samples, and also for failing to show hypersensitivity to tuberculin. These same authors suggested in those years that it might be a new clinical entity by itself, or a variation of papular rosacea with tuberculoid histopathology, rather than a clinical manifestation of TBC. Because of this, it stopped being considered as part of tuberculids and cutaneous TBC, and was later renamed as Lewandowsky's rosaceiform eruption, also called lupus miliaris disseminatus faciei (LMDF), acne agminata, and acnitis [36–39]. Through the years, in many reports lupus miliaris disseminatus faciei/Lewandowsky eruption has been related to TBC, sarcoidosis and rosacea [38–41], with four different histopathological forms previously defined (for LMDF) [41]. It is important to outline that studies that dismissed Lewandowsky's eruption as a form of TBC did not use the same technology that is now used for diagnostic purposes. This scenario might actually change

thanks to the new diagnostic techniques available, such as amplification of DNA from *M. tuberculosis* with PCR. In a number of studies [7–9], PCR has been shown to be the best diagnostic alternative when laboratory tests (e.g., immunohistopathology, Ziehl–Neelsen stains, Kinyoun, fluorochromic techniques using Auramine-Rhodamine for acid–alcohol-resistant bacillus, cultures, and detection of INF-gamma with QuantiFERON, and ELISpot with ELISA) are not suitable for diagnosis. PCR has been reported to have a global sensitivity up to 88% and specificity of 83% for the diagnosis of cutaneous TBC [7], but the accuracy of PCR varies depending on a number of factors such as geographic region, local bacterial concentrations and the DNA amplification technique used for PCR [6, 19, 42]. Some investigations have reported false negative results that might be explained by variations in the insertion sequence 6110 (IS6110) in strains of MTC, and because of a low copy number of IS6110 in *M. tuberculosis* strains described in some regions of the world [43]. PCR with hybridization for DNA amplification seems to be a good option because of the advantage that it offers in the reduction of false negatives [44]. Regarding false positive results, studies have suggested that instead of considering carryover contamination of *M. tuberculosis* DNA, the possibility of the presence of DNA sequences homologous to IS6110 in other microorganisms should be considered, such as in *Shigella sonnei*, *Escherichia coli*, and other Mycobacteria sp. [43]. For diagnostic PCRs, multiplexing by targeting two regions like IS6110 and hsp65 could be a good strategy for reducing false positives [43, 45], as demonstrated in Case 2. Even though these results must be taken into account, conclusions about diagnostic tools must be made based on systematic reviews of diagnostic test accuracy before applying it into clinical decisions. In this context, although PCR has shown to have high sensitivity and specificity, with good positive and negative predictive values, it is preferable to use it as a confirmatory test in patients with a high pre-test probability [6]. Both cases reported in this study bring about concern for reconsidering Lewandowsky's rosaceiform eruption as part of the spectrum of cutaneous TBC, as the presence of bacillus has been shown in skin samples and both patients responded positively to anti-TBC treatment. Due to the fact that these cases involve extrapulmonary TBC, and according to what is considered by authors such as Concha et al. [5], treatment should follow national schemes for these cases; this is based around a daily dose of isoniazid, rifampicin, and pyrazinamide for 2 months, and twice-a-week dose with isoniazid and rifampicin for 4 more months [5]. Also, second-line drugs in cases of resistance, such as quinolones, kanamycin, amikacin, capreomycin, ethionamide and cycloserine, must be taken into account; however, this was not necessary for the cases presented in this report. Clinical response in both cases was satisfactory, with complete resolution of cutaneous lesions at the end of treatment.

## CONCLUSION

Although results of tuberculin tests in both cases do not suggest hypersensitivity for TBC bacillus, it seems to be reasonable to revise the current diagnostic criteria of tuberculids as being cases with localized eruptions that are histopathologically compatible with tuberculid. It is possible that PPD skin tests of the second patient could be false negative (e.g., because of anergy status, drug use not properly informed, bad inoculation technique, etc.), which

complicates the interpretation of its result. It will be also interesting to once again discuss reconsidering Lewandowsky's rosaceiform eruption as a form of cutaneous TBC, and to carry out future analytic studies with sufficient sample sizes to determine the global diagnostic capacity of PCR in cutaneous TBC, especially in paucibacillary forms, and to compare the results of PCR from clinical, histopathological and analytic characteristics for the different presentations of cutaneous TBC.

## ACKNOWLEDGMENTS

All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. No funding or sponsorship was received for this study or publication of this article. All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

***Conflict of interest.*** R. Conlledo, A. Guglielmetti, M. Sobarzo, F. Woolvett, F. Bravo, S. González, F. Fich and V. Vial declare no conflict of interest.

***Compliance with ethics guidelines.*** Informed consent was obtained from all patients for being included in the study.

Special thanks to the Department of Anatomic Pathology and the Department of Dermatology, Pontifical Catholic University of Chile, for all their help and effort regarding diagnosis.



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