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A case series of dermatofibromas originating in leprosy lesions: a potentially misdiagnosed condition

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Background

Leprosy is a chronic and slowly progressive disease caused by *Mycobacterium leprae* that particularly affects the skin and peripheral nerves. Its clinical spectrum usually correlates directly with histological findings, reflecting the different grades of the host cell-mediated immune response against the bacilli (Massone et al. 2015; Cruz et al. 2017).

Particularly in hyperendemic regions, the appearance of nodular lesions within regressive leprosy lesions (RLL) may be clinically challenging (Massone et al. 2015). To distinguish among relapses, reinfections, histoid leprosy, keloidal reactions, immunologic reactions or even common cutaneous nodules, clinicians and pathologists should be aware of some important clinical-histological correlations. Furthermore, histological details may be useful, directly influencing important choices among strikingly different therapeutic options (Massone et al. 2015; Nath et al. 2015; Talhari et al. 2015).

Dermatofibroma (DF) is a common mesenchymal cutaneous lesion, also known as superficial benign fibrous histiocytoma (Yamamoto 2009; Han et al. 2011). Most cases are relatively easy to diagnose clinically. However, DFs are not usually thought to be the first differential diagnosis when facing lesions in a leprosy patient, even in those with RLL.

This study aimed to describe the clinical and histological patterns of a series of cases of DFs diagnosed in leprosy patients compared to those diagnosed in patients without leprosy and to discuss possible mechanisms and implications of these findings, as well as to review the most common differential diagnoses of lesions forming inside RLL.

Methods

In this case series study, all records with a confirmed histological diagnosis of DF were identified in a dermatology and leprosy outpatient referral unit in the southeastern region of Brazil from January 1, 2003 to June 30, 2017. All histologically confirmed DFs in this period in patients with and without leprosy were included. Patients with leprosy who developed DFs were divided according to whether they were undergoing polychemotherapy or postpolychemotherapy treatment. DFs originating in leprosy lesions were considered when the histological sections clearly showed the DF inserted in the context of a leprosy lesion in regression in the adjacent tissues. Patients who had more than one confirmed DF were also included. This study was reviewed by the local ethics committee and was therefore performed in accordance with the ethical standards set forth in the Declaration of Helsinki.

Leprosy was diagnosed using the Ridley-Jopling clinical classification (Ridley and Jopling 1966; Eichelmann et al. 2013; Cruz et al. 2017); leprosy reactions were classified as type 1 (T1Rs) and type 2 (T2Rs), according to the established criteria (Eichelmann et al. 2013; Kamath et al. 2014). Clinical data (sex, age, location of DF, classification of leprosy and leprosy reactions, time between the leprosy and DF diagnoses, and treatment of leprosy reactions) were retrieved through the review of medical records. The histological characteristics of DF were individually reviewed by a pathologist with experience in leprosy.

Serial sections were stained with hematoxylin-eosin (HE) and Fite-Faraco (FF). The samples were classified as DF (common fibrous histiocytoma) or its variants (lipidized, hemosiderotic, keloidal, granular cell, palisading, atrophic, clear cell, myxoid, lichenoid, signet-ring cell, epithelioid, aneurysmal, cellular, atypical, angiomatoid, pigmented, with multinucleated giant cells, and plexiform), according to the dominant pathological features (Luzar and Calonje 2010).

Immunohistochemistry (IHC) was performed in a single case, with the objective of demonstrating that the fusiform cells of the DF were not fusiform macrophages (CD68 - and Factor XIIIa +) and that the leprosy lesion in regression (CD68 + and Factor XIIIa -) could be observed in the periphery of the DF. This image is intended to allow better

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observation of the DF originating within the leprosy lesion and to facilitate the discussion of differential diagnoses (Fig. 1i to l). The IHC was performed according to a previously described method using the EnVision indirect method kit (Dako, California, USA) following the manufacturer's recommendations. The monoclonal antibodies used were anti-CD68 (KP1 clone, 1: 200, Abcam, Cambridge, UK) and anti-factor XIIIa (SP196 clone, 1: 100, Abcam, Cambridge, UK).

Numeric variables are described as the mean (SD) or median (interquartile range) according to the normality of their distribution, and categorical data are described as the frequency/percentage. Comparisons between groups were performed with parametric and non-parametric tests, as appropriate, and considered significant when $p < 0.05$.

Results

Out of 250 histologically confirmed DFs, 30 patients developed 37 lesions within previous leprosy lesions (13.5% of DF patients, 14.8% of DF lesions). In the same period, 4607 leprosy care consultations were performed in this referral unit. The mean age did not differ between the groups (43.6 ± 14.6 years; Student's *t*-test, $p = 0.95$). There were more female patients than male patients without leprosy (3:1), while more men than women had leprosy (2:1). The time between the diagnoses of leprosy

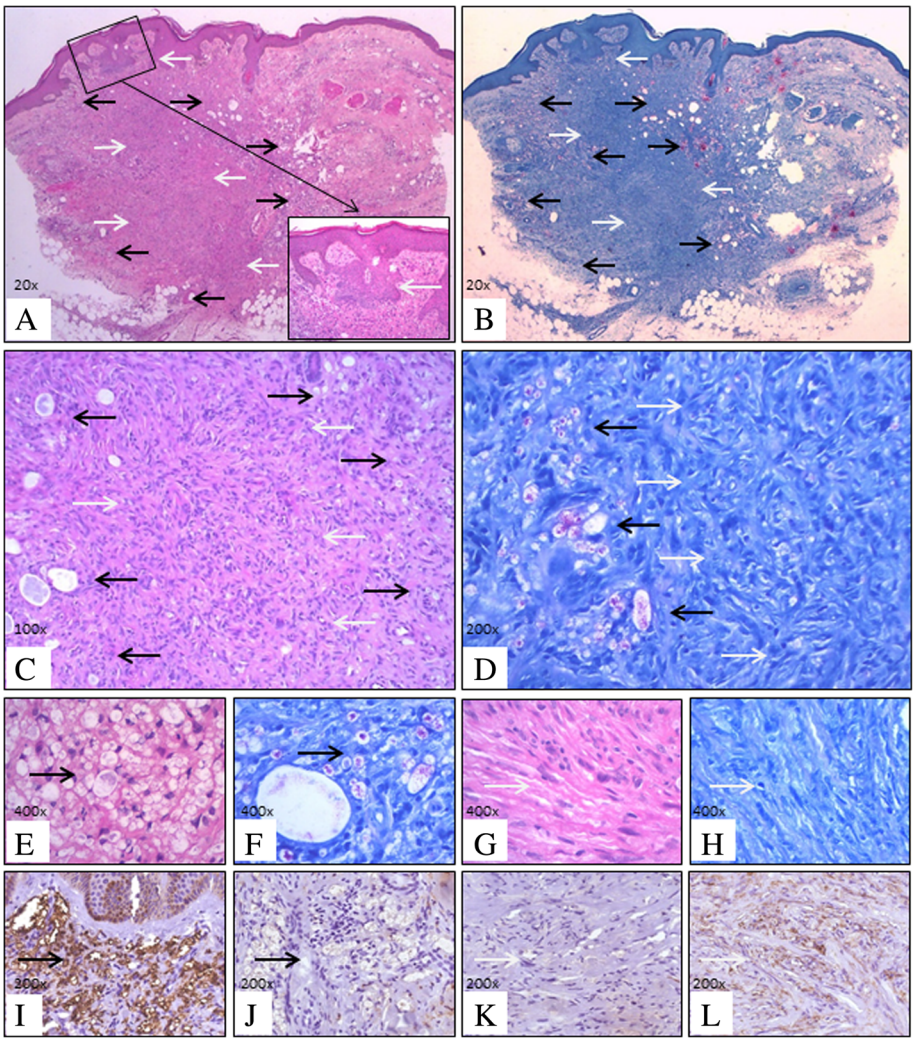

Fig. 1 Representative panel of dermatofibroma originating in a leprosy lesion: **a**, **c**, **e**, and **g** Hematoxylin-eosin-stained histological section showing the dermatofibroma in the center (light arrows) and the leprosy lesion in regression at the periphery (dark arrows); **b**, **d**, **f**, and **h** histological section for bacilloscopy (Fite-Faraco) showing absence of bacilli in the dermatofibroma (clear arrows) and presence of fragmented bacilli in the leprosy lesion in peripheral regression (dark arrows); **i**, **j**, **k**, **l** basic immunohistochemical panel – expression of anti-CD68 (**i**) in leprosy lesion macrophages and the absence of anti-factor XIIIa expression in the same macrophages (**j**); the absence of anti-CD68 expression (**k**) and the expression of anti-factor XIIIa in dermatofibroma cells

and DF ranged between 12 to 288 months, with a median of 36 (interquartile range: 24.0–65.2) months.

Of the 30 leprosy patients with DF, 16 were diagnosed with LL, and 14 had borderline leprosy (BL). In this set of patients with DFs in RLLs, there were no other forms of leprosy. Almost all patients (28/30) had T2Rs (93.3%). The drugs most commonly used to treat T2Rs are described in the appendices. The mean number of DFs was not different among patients with and without leprosy (chi-squared test, $p = 0.89$). Table 1 shows the location and distribution of the DFs between groups.

All DFs in RLLs were common DFs, and three of them had the histologic patterns characteristic of the atrophic variant. They were located in the dermis/subcutaneous tissue, surrounded by a halo of foamy macrophages, contained fragmented bacilli, identified by FF staining, and showed the RLL in the periphery; the DF occupied the central portion of the lesion (Fig. 1).

Samples were classified as common DF ($n = 213$) in the remaining 204 patients. The following variants were identified in nine patients without leprosy, according to the dominant pathological features: four lipidized, one aneurysmal, one atrophic, two pigmented, and one with multinucleated giant cells. In the patients with leprosy, DFs were excised to rule out different clinical scenarios, such as reactions, recurrence or reactivation of leprosy, histoid leprosy, DF, keloid, and common nevus, among others.

Discussion

The controversy of whether DF is an inflammatory/reactive or neoplastic lesion is ongoing in the literature. Molecular studies have shown that some of these lesions may demonstrate gene fusion involving PRKCB and PRKCD, suggesting a neoplastic nature. Others, however, report the development of DFs in lesions associated with local trauma, insect bites and folliculitis (Glusac et al. 2018).

In this study, leprosy patients with DFs exclusively had LL and BL; only two patients did not develop T2R. There were high incidence rates of T2R and the development of DFs within RLL. Both T1R and T2R are characterized by abrupt inflammatory episodes that develop on cutaneous-neural leprosy lesions that are sometimes intense and destructive that intersperse in the evolution of disease, often after initiation of treatment (Fleury 2000). They are characterized by the influx of macrophages, lymphocytes and other cells in T1R, as well as of neutrophils in T2R, sometimes forming microabscesses. It is possible that immunologic disorders in leprosy lesions caused by chemotherapy and reactional lesions (T2R), particularly in anergic or partially anergic patients, may induce the development of DFs and other reactive cutaneous lesions.

In endemic areas, the majority of leprosy diagnoses can be made clinically, complemented by skin smear and histology results (Ramos-e-Silva and Rebello 2001; Eichelmann et al. 2013; Talhari et al. 2015). Nevertheless, the distinction among the main lesions forming inside RLLs based only on clinical aspects may be challenging.

Relapse is far less common than immunologic reactions (especially *erythema nodosum leprosum*) (Kaimal and Thappa 2009), but considering the burden of relapse and histoid leprosy, their signs and symptoms should be

Table 1 Distribution of dermatofibromas (DF) in a sample of 222 patients with and without leprosy

Body location of DF	Leprosy patients with DF, count (%)	Non-leprosy patients with DF, count (%)	Total
Cervical	0 (0%)	1 (0.5%)	1
Face	0 (0%)	2 (1.0%)	2
Thorax	0 (0%)	9 (4.7%)	9
Abdomen	0 (0%)	1 (0.5%)	1
Dorsum	4 (13.3%)	27 (14.1%)	31
Thigh	10 (33.3%)	35 (18.2%)	45
Arm	7 (23.3%)	31 (16.1%)	38
Hand	1 (3.3%)	5 (2.6%)	6
Buttock	1 (3.3%)	1 (0.5%)	2
Knee	2 (6.7%)	2 (1.0%)	4
Forearm	1 (3.3%)	21 (10.9%)	22
Leg	9 (30.0%)	54 (28.1%)	63
Elbow	1 (3.3%)	9 (4.7%)	10
Shoulder	0 (0%)	5 (2.6%)	5
Foot	1 (3.3%)	4 (2.1%)	5
Perineum	0 (0%)	1 (0.5%)	1
Total	30	192	222

primarily investigated when lesions form inside RLLs. It is important that a hypothesis of relapse or reinfection should only be considered after completion of PCT (Becx-Bleumink 1992; Kaimal and Thappa 2009), the details of which are shown in Table 2.

In its classic form, a DF is an ill-defined dermal lesion characterized by a variable number of spindle cells, collagen bundles, inflammatory cells and associated epidermal, melanocytic and pilosebaceous hyperplasia. The stroma is typically collagenous or sclerotic. The inflammatory infiltrate at the periphery may contain macrophages forming some giant multinucleated cells or lipophagous types. The papillary dermis is often spared, resulting in a "grenz zone" between the lesion and the overlying epidermis, which is frequently hyperplastic (Doyle and Fletcher 2013).

When DFs are submitted to bacilloscopic evaluation using F-F staining, their spindle cells do not have bacilli in the cytoplasm. Multifragmented bacilli are observed in the macrophages that are part of the RLL and are arranged in the periphery of the DFs. Both findings were used to rule out the possibility of active leprosy. Reactional episodes are easily ruled out from the histological point of view by the absence of reaction characteristics in these samples of leprosy lesions in regression with associated DFs.

There is no influx of new cells, particularly lymphocytes and macrophages forming new granulomas, as is observed in T1R, or neutrophils forming microabscesses, as is seen in T2R. Keloids, nevi, neurofibromas and other cutaneous lesions forming inside RLL are usually clinically indistinguishable, which highlights the importance of histologic examination.

The histological characteristics of the DFs may be helpful in the differentiation between DF and nevi or keloids. In our experience, changes in fibroblasts and collagen fibers in the dermis may be noticed in RLL, particularly after T2R; these findings were found to occur after the initiation of PCT and not in treatment-naive patients. In general, fibroblasts have more prominent nuclei with nucleoli and increased numbers of collagen fibers. Collagen bands are formed involving regressing granulomas and multinucleated giant cells. These histological characteristics are different from those of DFs, even when considering those with atrophic patterns.

The most important differential diagnoses are histoid leprosy and DF with lipidized areas. Histoid leprosy is characterized by well-delimited papular or nodular lesions, similar to DF, in multibacillary leprosy patients who discontinued treatment or had resistance to sulphone (Wade 1963). The histology shows a proliferative pattern of spindle cells, similar to DF or fibrosarcoma, but the spindle cells are macrophages containing large numbers of bacilli and are easily recognized by FF staining (Wade 1963). Bacilloscopy (FF) demonstrating the absence of bacilli in the spindle cells of the DF at the

Table 2 Clinical and histopathological characteristics of the main leprosy lesions considered as diagnostic hypotheses that resulted in biopsies with a subsequent diagnosis of dermatofibromas originating in leprosy lesions

	Relapse	T1R[a] (RR)[b]	T2R[c] (ENL)[d]	Histoid leprosy	Drug resistance
Course	Recurrence 1 year or more after withdrawal of treatment	Usually within 6 months of withdrawal of treatment; in recurrent reactions, up to 2 years	Can occur any time during the course of leprosy, but is most common within 1 year of starting PCT	Patients who discontinued treatment or had resistance to sulfone	Initial amelioration followed by halt or worsening
Leprosy lesions	All types	BT, BB, BL	LL side (LL and BL)	LL side (LL and BL)	LL side (LL and BL)
Skin lesions	Increase in size and extent of existent lesion(s); new lesion(s); reappearance of lesions over old lesions; ulcerations not seen	Existing lesions become tumid and erythematous; distribution: locations of existing lesions; ulcerations seen in severe reactions	New erythematous dermal and/or subcutaneous nodules; painful and tender; distribution: upper and lower extremities, trunk, face	Skin-colored papules and nodules; bacillary proliferation and morphologically solid bacilli within fusiform macrophages	Appearance of new lesions with bacillary proliferation and morphologically solid bacilli
Nerves	Nerve involvement; no spontaneous pain; tenderness on pressure; sensory and motor deficits slow and creeping; bacillary proliferation	Acute painful neuritis; nerves exquisitely tender; nerve "abscess" (caseous necrosis); sudden paralysis of muscles and increase in extent of sensory loss	Similar to T1R, but with influx of neutrophils and formation of microabscesses and absence of caseous necrosis	None	Bacillary proliferation
Treatment	Retreatment with standard PCT or drug change if resistance is detected	Prednisone (start at 0.5–1.0 mg/kg) NSAIDs Azathioprine Cyclosporine	Thalidomide (start at 100–200 mg daily) Clofazimine Prednisone Pentoxifylline TNF-alfa inhibitors	Retreatment with standard PCT or drug change if resistance is detected	Retreatment. New drugs are used according to the definition of which of them previously used resulted in resistance by *M. leprae*

LL lepromatous, *PCT* polychemotherapy, *I* indeterminate, *TT* tuberculoid, *BL* borderline lepromatous, *BB* borderline borderline, *BT* borderline tuberculoid, *NSAIDs* nonsteroidal anti-inflammatory drugs

[a]Type 1 reactions; [b]Reversal reaction; [c]Type 2 reaction; [d]*erythema nodosum leprosum*

center of the lesion and the presence of fragmented bacilli in the macrophages located in the periphery distinguishes a lesion of histoid leprosy from a DF originating in a leprosy lesion (Fig. 1b, d, f and h).

Regarding DFs with lipidized macrophages, bacilloscopy (FF) allows these to be distinguished from DF originating in leprosy lesions. In these cases, the lipidized macrophages of DF do not contain bacilli, whereas in DF originating in leprosy lesions, there are fragmented bacilli in the macrophages. Additionally, it is important that the pathologist is familiar with the histological characteristics that differentiate the lipidized macrophages of DF and the multivacuolated macrophages that make up the granulomas in leprosy lesions. Generally, macrophages in leprosy lesions have vacuoles of various sizes that contain fragmented bacilli, which are easily identified by FF staining. The lipidized macrophages of DFs have a cytoplasm with numerous small regularly sized vacuoles, with an absence of bacilli revealed by FF staining. For the differential diagnosis of *dermatofibrosarcoma protuberans* (DFSP), immunohistochemistry for markers such as CD34 and factor XIIIa is useful, with the expression of CD34 and negativity for factor XIIIa indicating DFSP (Fig. 1) (Prieto et al. 1995; Wilk et al. 2004). In addition to the immunohistochemical profile described above, the presence of multivacuolated macrophages and the induction of epithelial hyperplasia with hyperpigmentation of the epidermis overlying the lesion are two important characteristics present in DFs and absent in DFSP.

Conclusions

In conclusion, within leprosy lesions, DF seems to be particularly common in patients in the lepromatous (BL and LL) spectrum who have completed polychemotherapy and among those who develop reactional episodes. Pathologists, especially those working in countries where leprosy is endemic, should be alert to identifying DF originating in RLL and avoid erroneous diagnoses such as histoid leprosy or DF with lipidized macrophages that may be harmful to patients by inducing leprosy treatment changes or delaying the diagnosis of leprosy.

Additional file

Additional file 1: Table S1. Types and frequency of drugs used to treat episodes of type 2 reaction in leprosy patients who developed 37 lesions of dermatofibroma within leprosy lesions in regression. (DOCX 20 kb)

Abbreviations

BL: Borderline leprosy; DF: Dermatofibroma; DFSP: *Dermatofibrosarcoma protuberans*; FF: Fite-Faraco; HE: Hematoxylin-eosin; IL: Interleukin; LL: Lepromatous leprosy; RLL: Regressive leprosy lesions; T1R: Type 1 reaction; T2R: Type 2 reaction

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its Additional file 1: Table S1].

Authors' contributions

Conception and design of the study: CTS, PAW. Acquisition of data: DCJ, PYM. Analysis and/or interpretation of data: CTS, PAW, PYM. Drafting the manuscript: CTS, PAW, WAB. Revising the manuscript critically for important intellectual content: CTS, PYM, PAW. Approval of the version of the manuscript to be published: CTS, DCJ, PAW, PYM, WAB. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Instituto Lauro de Souza Lima. Written informed consent to participate was previously obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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